STUDIES ON THE SYNTHESIS AND REACTIVITY OF NITROGEN HETEROCYCLES DERIVED FROM ORTHO-NITROBENZENE DERIVATIVES

by

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To my wife, Anne,

and my parents.

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Dr. A.J. Bellamy, University of Edinburgh.

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SUMMARY

A series of 2-nitrophenacylidene phenylhydrazones has been prepared by the coupling of benzenediazonium chloride with the appropriate active methylene compounds. The base-catalysed cyclisation of the phenylhydrazones to give 3-substituted 1-phenylcinnolin-4(1H)-ones is described and mechanisms accounting for the formation of these products are discussed. Attempts to extend the scope of the cyclisation are described, including the synthesis of some 2-nitrophenacylidene oximes, one of which was successfully cyclised to give 3-cyanobenz-1,2-oxazin-4-one.

The attempted syntheses of an N-hydroxyacridone by the cyclisation of 3-methoxy-2'-nitrobenzhydrol and of N-hydroxybenzoxazolone and N-hydroxybenzthiazolone by the reduction of ethyl 2-nitrophenylcarbonate and 2-nitrothiocyanatobenzene, respectively, were unsuccessful. An alternative approach to the N-hydroxybenzthiazolone by the base-catalysed cyclisation of 2-nitrophenylthioacetonitrile was likewise unsuccessful. The attempted base-catalysed cyclisations of an N-(2-nitrobenzyl)aminoacetonitrile and an N-cyanomethyl-2-nitrophenyl-sulphenamide were also unsuccessful.

The conversion of 1-acyloxy-3-acetyl-6-chloro-2-methylquinolin-4(1H)-ones into their 2-acyloxymethyl isomers by heating in the appropriate carboxylic acid is described and mechanisms accounting for these rearrangements are discussed. 6-Chloro-3-hydroxy-2-methyl-1-(toluene-4-sulphonyl)quinolin-4(1H)-one is shown to be the product of the reaction of 3-acetyl-6-chloro-1-hydroxy-2-methylquinolin-4(1H)-one with toluene-4-sulphonyl chloride in the presence of pyridine and a mechanism is proposed to account for its formation.

A series of 1-sulphonyloxyquinazoline-2(1H),4(3H)-diones has been prepared by the reaction of the appropriate N-hydroxyquinazolinedione with toluene-4-sulphonyl chloride or methanesulphonyl chloride and their thermal rearrangement to give mixtures of their 6- and 8-sulphonyloxy isomers has been demonstrated. Mechanisms for these thermal rearrangements are proposed and discussed. Attempts to extend the scope of rearrangement by preparing quinazolinediones with a variety of 1-acyloxy or 1-aryloxy substituents are also described. The attempted thermal rearrangement of 2-phenyl-3-(toluene-4-sulphonyloxy)quinazolin-4(3H)-one was unsuccessful.

The reaction of 4-hydroxy-1-methylquinoxaline-2(1H),3(4H)-dione with toluene-4-sulphonyl chloride in dimethylformamide has been investigated and mechanisms to account for the formation of the 7-chloro and 7-hydroxyquinoxaline products are discussed. Quinoxalin-7-ylpyridinium betaines are shown to be the products from the reactions of toluene-4-sulphonyl chloride with the 4-hydroxy-1-methylquinoxalinedione and its 1-benzyl analogue in the presence of pyridine. Attempts to extend the scope of this reaction to other N-hydroxyquinoxalinediones were unsuccessful. Quinoxalin-7-ylpyridinium salts or betaines are also shown to be products of the reactions of a series of 3-phenylquinoxalin-2(1H)-one 4-N-oxides with toluene-4-sulphonyl chloride in the presence of pyridine. Mechanisms accounting for the formation of these products are discussed.

Cleavage of the pyridinium salts or betaines by heating under reflux with piperidine in methanol gives the corresponding 7-aminoquinoxalines. The reactions of 7-methylquinoxaline 4-N-oxides and 1-hydroxyquinoxaline 4-N-oxides with toluene-4-sulphonyl chloride in the presence of pyridine are also described and mechanisms accounting for the formation of the products are discussed.

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APPENDIX

(1)
(2)
(3)
(4)
(5)
(6)
(7)
NO_2
CO_2Et
$(NH_4)_2S$
OH
O

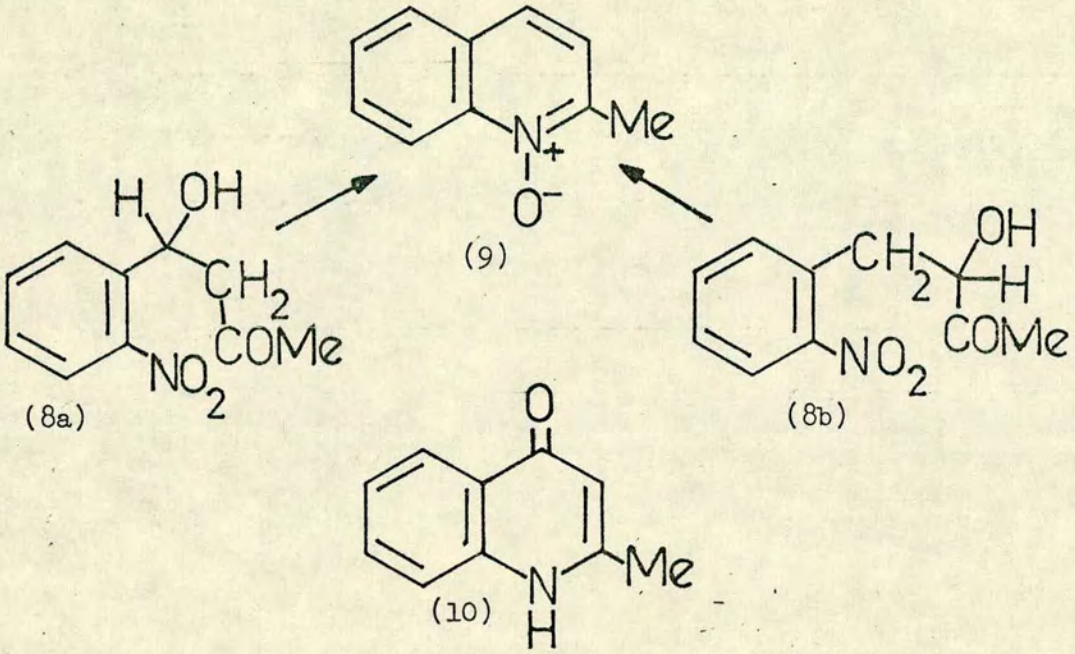
PART 1

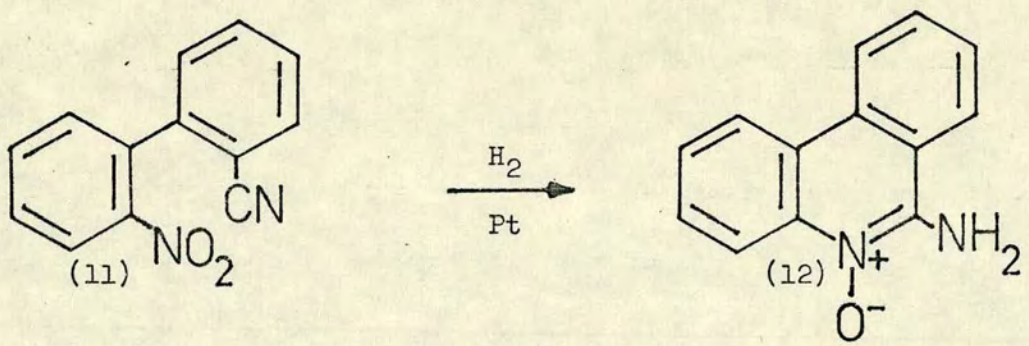
The Synthesis of Heterocycles from Ortho-Nitrobenzene Derivatives.

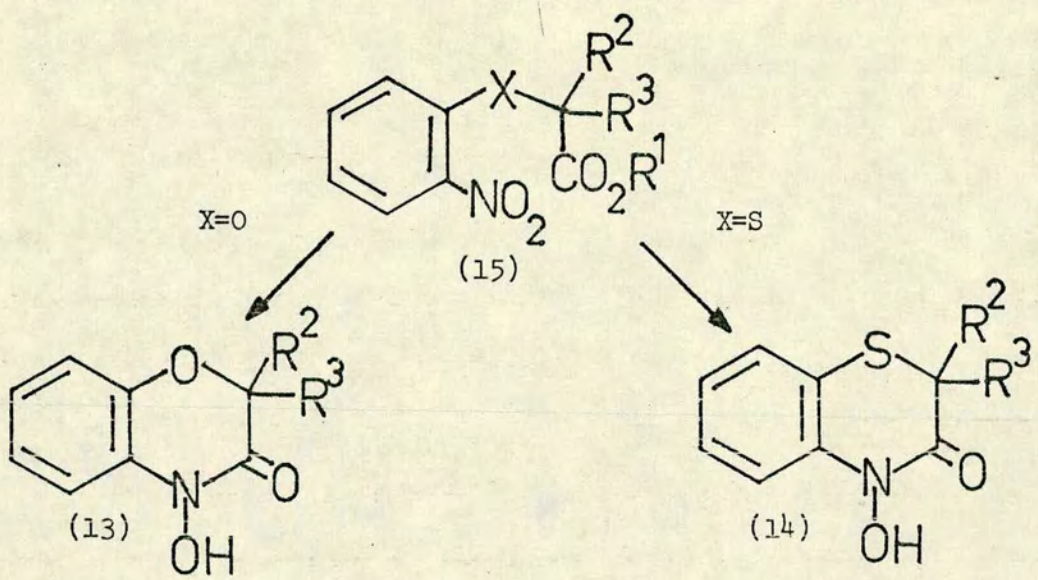
Ortho-substituted nitrobenzene derivatives have been extensively used as starting materials for the synthesis of a variety of heterocycles. Most commonly the reduction of such substrates, using a variety of reducing agents, leads by cyclisation of amino- or hydroxylamino-intermediates to benzaza-heterocycles or their N-oxides. However, reduction is not the only synthetic method available for the formation of nitrogen heterocycles from ortho-nitrobenzene derivatives. Cyclisation is also possible by direct interaction of the nitrogen atom of the intact nitro group with a nucleophilic centre in the side chain [(1)→(2)] or by electrophilic attack by the side chain on an oxygen atom of the nitro group [(4)→(5)]. These processes may be base- or acid-catalysed reactions or photochemically induced. Cyclisation by intramolecular displacement of the nitro group by a nucleophilic centre in the side chain [(1)→(3)] is also possible. All of these processes can lead to interesting heterocycles which are frequently inaccessible by other methods.[1,2]

A. The Cyclisation of Ortho-Nitrobenzene Derivatives by External Reduction of the Nitro Group

The earliest synthesis of this type was carried out in 1881 by Friedlander and Ostermaier[3] who on reducing ethyl ortho-nitrocinnamate (6) with ammonium sulphide obtained a product, "oxycarbostyril", which was subsequently shown by Friedlander[4] to be carbostyril 1-oxide (7). In the earlier studies of reactions of this type, the products were not generally recognised as N-oxides or cyclic hydroxamic acids and many of the original structures proposed have since had to be reassigned.


Me
N+
O-
(9)
H OH
CH2
COMe
NO2
(8a)
CH2 OH
H
COMe
NO2
(8b)
O
Me
N
H
(10)


CN
NO2
(11)
H2
Pt
NH2
N+
O-
(12)

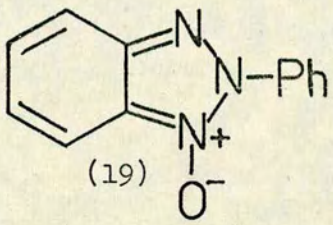

X
R2
R3
CO2R1
NO2
(15)
X=O
X=S
O
R2
R3
N
O
OH
(13)
S
R2
R3
N
O
OH
(14)

Thus, reduction of the nitro compounds (8 a or b) with zinc in acetic acid was reported[5] to afford an "isomer" of 2-methylquinolin-4(1H)-one (10). Later work showed the product to be quinaldine N-oxide (9) since it was identical to the product obtained by direct N-oxidation of quinaldine[6]. A wide variety of reducing agents can be used to effect cyclisations of this type including metal-proton-donor reagents (e.g. zinc and acetic acid[5]; zinc and ammonia[7]), stannous chloride[8] and sodium or ammonium sulphide[3]. Hydrogenation in the presence of palladium, platinum or nickel catalysts[9] or using sodium borohydride in the presence of palladium charcoal[10] is also successful. Thus, catalytic hydrogenation over platinum of suitable 2-substituted 2'-nitrobiphenyls [e.g. (11)] gives good yields of phenanthridine N-oxides [e.g. (12)][9].

In most of the above-mentioned reactions, formation of the N-oxide is accompanied by formation of the reduced heterocycle which in some cases is the major product. Since the N-oxides are often stable to reduction under the conditions employed for cyclisation, the reduced heterocycles are probably formed by complete reduction of the nitro group in the starting material to the corresponding amine with subsequent cyclisation.

Hydroxamic acids of the benzoxazine series (13)[11] and the benzothiazine series (14)[12] which show antibacterial activity have been prepared by the reduction of the appropriate 2-nitrophenoxyacetic ester (15; X = O) or 2-(2'-nitrothiophenyl)acetic ester (15; X = S) respectively.

Reductive cyclisation of 2-nitrobenzene derivatives is of particular importance in the synthesis of benzazole N-oxides which cannot, in general, be obtained by direct N-oxidation of the parent heterocycle. The formation of benzimidazole N-oxides (16) by mild



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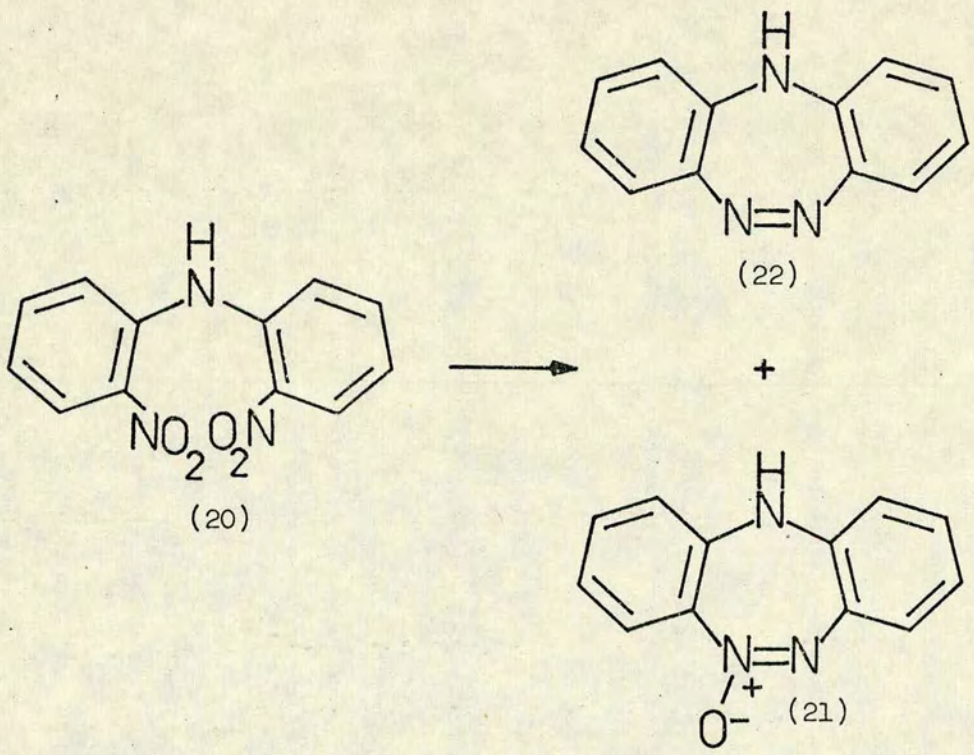
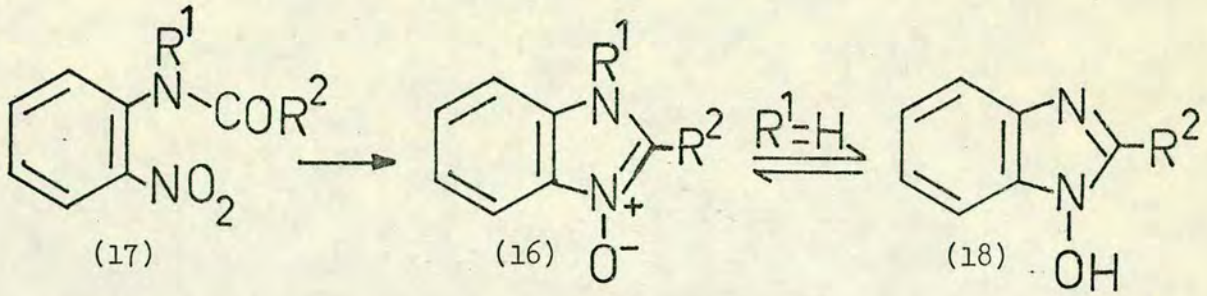


(20)

(22)

(21)

reduction of 2-nitroanilides (17) using tin[13] or zinc[14] and hydrochloric acid, or ammonium sulphide[15] was first described by von Niementowski. N-Hydroxybenzimidazoles (18) which are



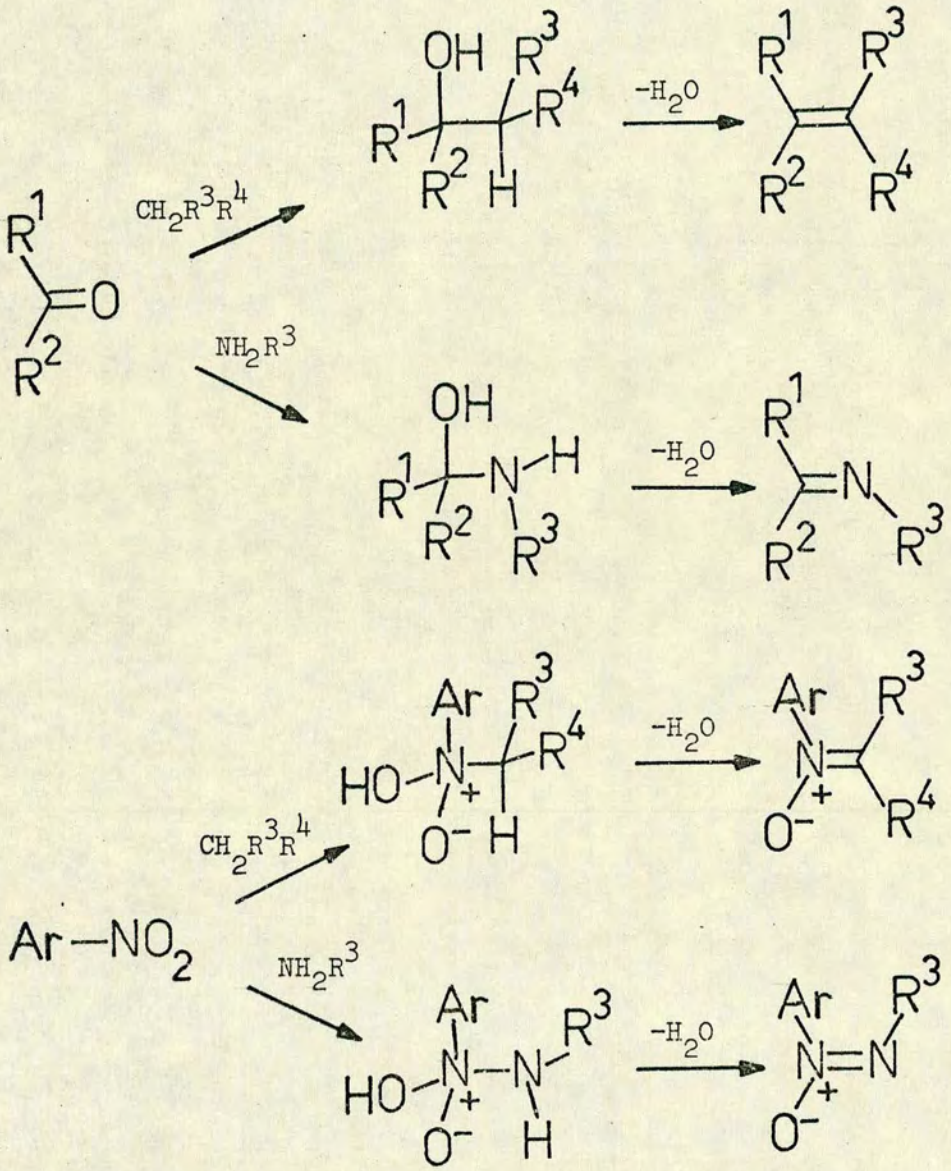
(17) (16) (18)

in tautomeric equilibrium with benzimidazole N-oxides (16; R^1 = H), are the products if a 2-nitroanilide (17; R^1 = H) is reduced whereas reduction of an N-substituted 2-nitroanilide (17; R^1 = alkyl or aryl) affords a 3-substituted benzimidazole 1-oxide (16; R^1 = alkyl or aryl) which is not capable of tautomerism. However, this type of cyclisation suffers from the disadvantage that it is only possible to introduce alkyl or aryl groups[16] and not functional groups (e.g. keto, ester or cyano groups) into the 2-position.

The reduction of 2-nitroazoxybenzene using ammonium sulphide to give a product which was later identified by Werner and Stiasny[17] as 2-phenylbenzotriazole 1-oxide (19) was first described by Zinin in 1860.[18] A number of substituted benzotriazole 1-oxides have been prepared similarly.[17,19]

Reductive cyclisation of 2-nitrobenzene derivatives to give seven-membered rings has also been described recently. Thus reduction of the diphenylamine (20) gives a mixture of 11H-dibenzo[1,2,5]triazepine 5-oxide (21) and the parent heterocycle (22).[20]

B. The Cyclisation of Ortho-Nitrobenzene Derivatives in the Absence of External Reducing Agents.

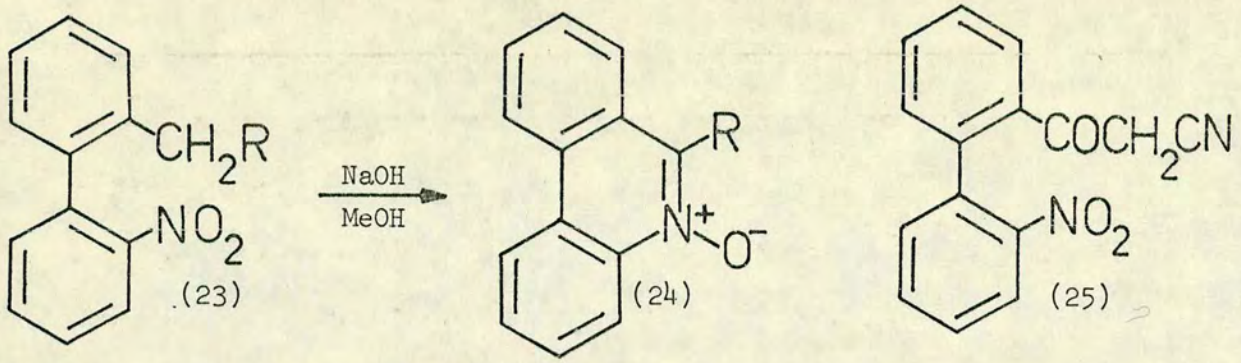


Scheme 1

(i) Cyclisations involving Aldol-type Condensation between the Nitro Group and an Ortho-Side Chain in Nitrobenzene Derivatives.

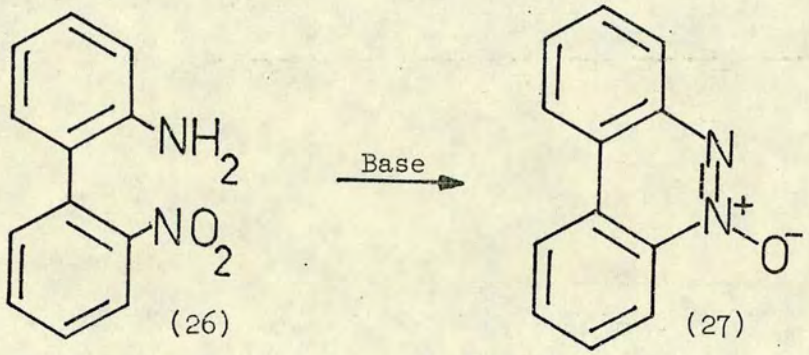
The chemistry of the carbonyl group and the chemistry of the nitro group show certain similarities, one of which is the apparent ability of both to act as the electrophilic centre in reactions of the aldol type (Scheme 1). Carbon- or nitrogen-based nucleophiles may be involved in these nitro group condensations which may be acid- or base-catalysed. No unambiguous examples of intermolecular aldol condensations involving aromatic nitro groups appear to have been reported. On the other hand, intramolecular aldol condensations involving aromatic nitro groups are more common presumably due to the more favourable steric situation involved. The products of such intramolecular condensations are often N-oxygenated heterocycles which are otherwise synthetically inaccessible. This is particularly true in the case of such reactions leading to N-oxygenated benzazoles (see later). The formation of N-oxygenated heterocycles by intramolecular aldol-type condensations of aromatic nitro groups also has the advantage (unlike synthesis by peracid oxidation) that the position of the N-oxide group is known with certainty.

Perhaps the simplest examples of the aldol-type condensations of aromatic nitro groups are found in the base-catalysed reactions of certain 2-nitrobiphenyl derivatives.[21,22] Attempted saponification of the ester (23a) with sodium hydroxide and methanol gives a mixture of the phenanthridine-6-carboxylic acid 5-oxide (24b) and its methyl ester (24a). Cyclisation of the benzoyl compound (23e) gives phenanthridine 5-oxide (24g) presumably by cyclodehydration and hydrolytic removal of the benzoyl group as benzoic acid which is also isolated. In



(23) (24) (25)

a) CO_2Me e) COPh i) Br
b) CO_2H f) SO_2Ph j) Ph
c) $CONH_2$ g) H
d) CN h) OH



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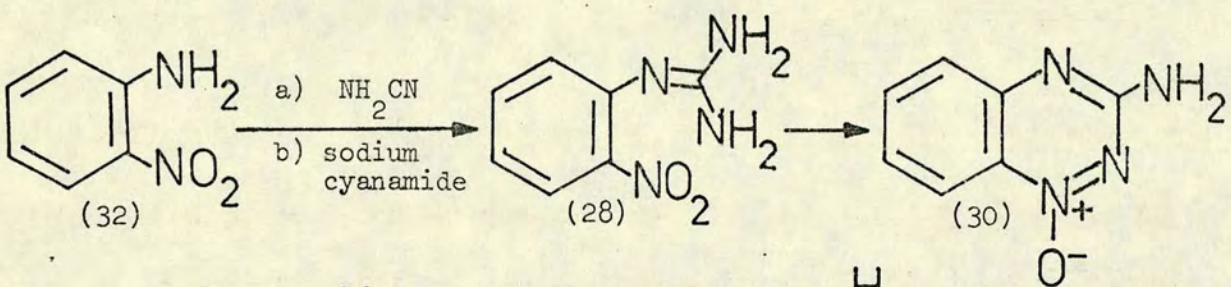
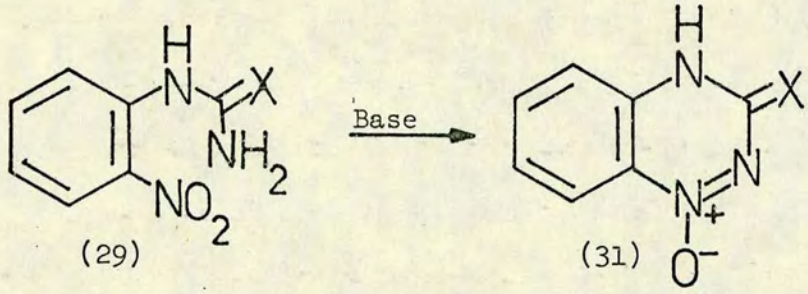


(32) (28) (30)



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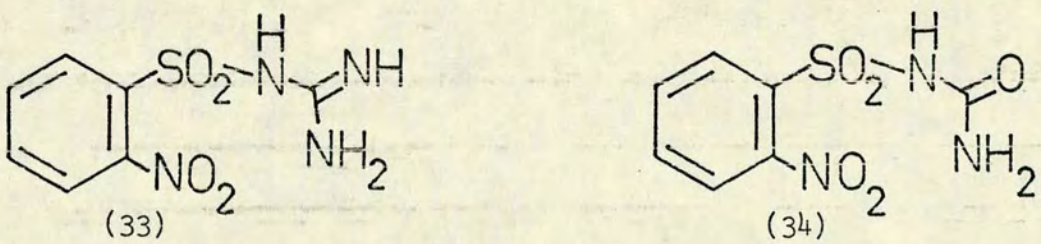
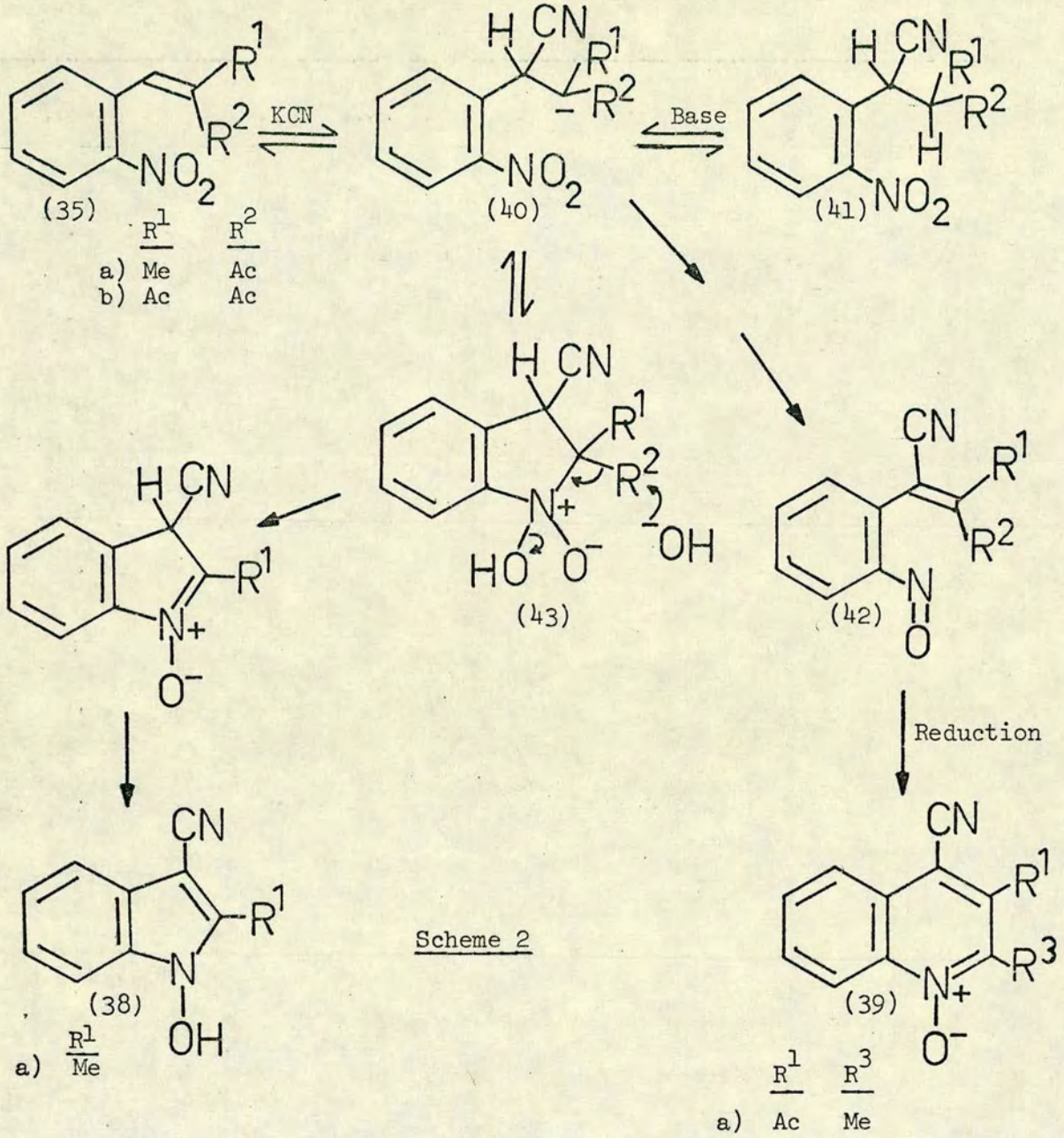


(33) (34)

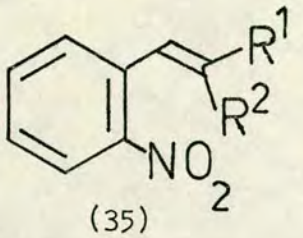
contrast, cyclisation of the benzenesulphonyl compound (23f) affords not the expected N-oxide (24f) (which is apparently unstable under the reaction conditions) but 5-hydroxyphenanthridone which is tautomeric with the N-oxide (24h). The controlling factor in all of these reactions appears to be the activation of the methylene group since the biphenyls (23b and g-j) fail to undergo cyclisation under basic conditions. However, steric factors also appear to be important since the nitro compound (25) which can only form a seven-membered ring fails to undergo cyclisation. 2-Amino-2'-nitrobiphenyl (26) also undergoes base-catalysed cyclisation in high yield giving benzo[c]cinnoline 5-oxide (27)[22] although in this case the aldol-type condensation is more sluggish than in the cases of the biphenyls (23).

The base-catalysed cyclisation of 2-nitrophenylguanidine (28) and 2-nitrophenylurea (29; X = O) to give 3-aminobenzo-1,2,4-triazine 1-oxide (30) and benzo-1,2,4-triazin-3(4H)-one 1-oxide (31; X = O) respectively was first discovered by Arndt in 1913[23] and later extended to include the synthesis of benzo-1,2,4-triazine-3(4H)-thione 1-oxide (31; X = S) from the corresponding thiourea (29; X = S).[24] Since then, this type of reaction has assumed great importance for the synthesis of benzo-1,2,4-triazine 1-oxides and a number of extensions and modifications have been reported. Often the 2-nitrophenylguanidine (e.g. 28) is generated *in situ* by the reaction of the corresponding 2-nitroaniline derivative (e.g. 32) with cyanamide[25] or sodium cyanamide[26], followed by base-catalysed cyclisation. The 2-nitrophenylguanidine (28) and the 2-nitrophenylurea (29; X = O) may also be generated *in situ* by Smiles Rearrangement of the sulphonylguanidine (33)[27] and the sulphonylurea (34)[28] respectively.


KCN
Base
Reduction
(35)
(40)
(41)
(42)
(43)
(38)
(39)
R^1 R^2
a) Me Ac
b) Ac Ac
R^1
a) Me
R^1 R^3
a) Ac Me

Scheme 2

The use of potassium cyanide as the base in the cyclisations of 2-nitrobenzylidene derivatives of the type (35), 2-nitrobenzylidene anilines (36) and benzylidene-2-nitroaniline (37) to give N-oxygenated



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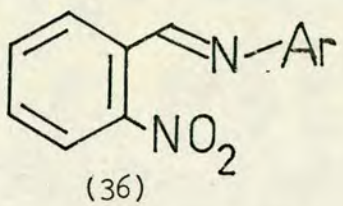

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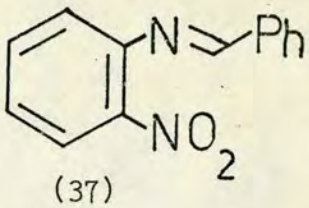
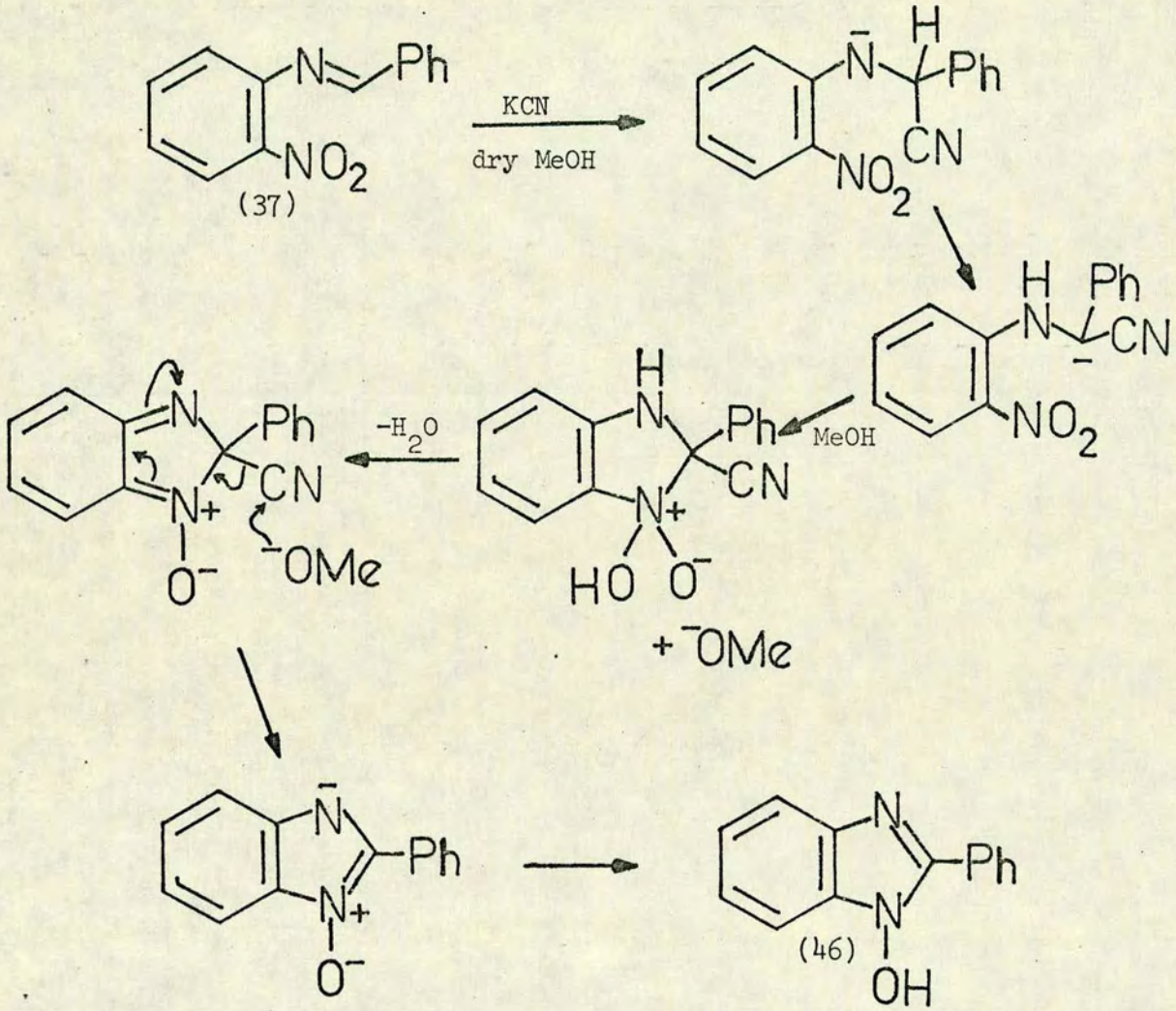


(37)

benzazoles has proved interesting and very successful.

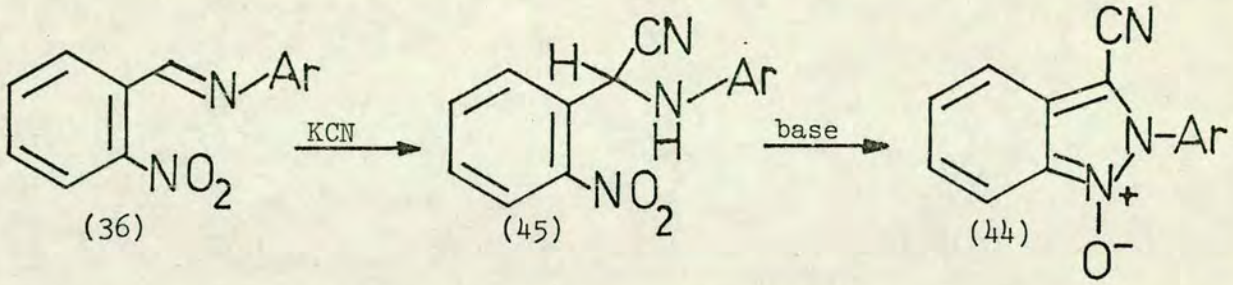
The work of Loudon and his co-workers[29,30] and later Sword[31] on the cyanide-catalysed transformations of 2-nitrobenzylidene compounds (35) and related reactions has shown that the products are N-hydroxyindoles (38) or quinoline 1-oxides (39) or mixtures of both. The results can be explained by the mechanism shown in Scheme 2. The nature of the products appears to be dependent on the stability of the anion (40) which can be formed either by addition of cyanide ion to the benzylidene compound (35) or by the action of base on its hydrogen cyanide adduct (41). In (40), when R^1 is an alkyl group and R^2 is an electron-withdrawing group (e.g. Ac, Bz, CN), N-hydroxyindoles (38) are formed exclusively, by intramolecular aldol-type condensation in the anion (40) with subsequent base-catalysed elimination of the activating group, R^2 (43). Thus, the cyanide-catalysed cyclisation of (35a)[31] affords 3-cyano-1-hydroxy-2-methylindole (38a) with elimination of the acetyl group. When the stability of the anion (40) is increased by the presence of two electron-withdrawing groups, other pathways assume greater importance e.g. conversion in strong base of the anion (40) into the nitroso compound (42) which undergoes reduction in the reaction medium and subsequent cyclisation to give quinoline 1-oxides (39).



Scheme 3

Thus, 2-nitrobenzylideneacetylacetone (35b) is cyclised in ethanolic potassium cyanide to yield the quinoline 1-oxide (39a), exclusively.[31]

A closely related reaction is the potassium cyanide-catalysed cyclisation of 2-nitrobenzylidene anilines (36) to 2-aryl-3-cyanoindazole 1-oxides (44).[32,33] It seems likely that

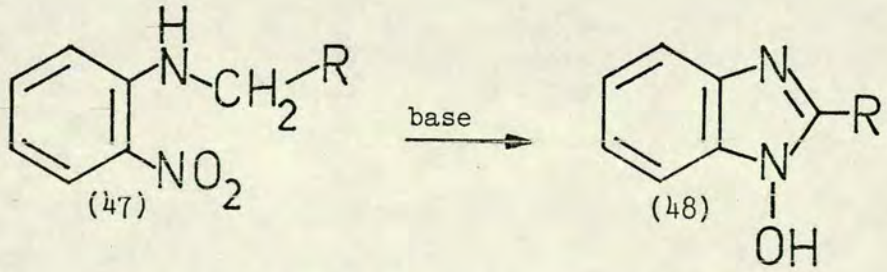


(36) (45) (44)

the intermediate in this reaction is the nitrile (45) since the indazole (44) is formed from (45) on treatment with base.[34]

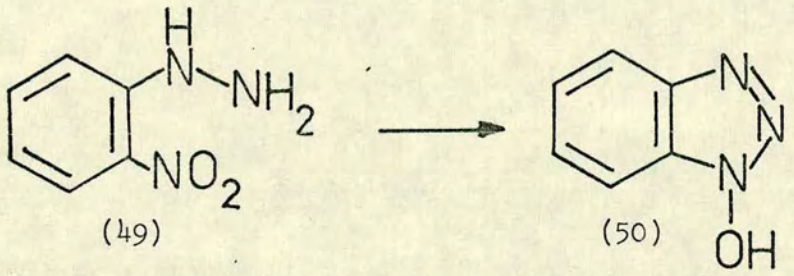
Recently, Marshall and Smith[35] have observed the formation of 1-hydroxy-2-phenylbenzimidazole (46) in the cyanide-catalysed cyclisation of N-benzylidene-2-nitroaniline (37) and, by analogy with the above syntheses of indoles and indazoles, have proposed the mechanism for this transformation shown in Scheme 3.

A large number of benzimidazole N-oxides or the tautomeric N-hydroxybenzimidazoles have been prepared by base-catalysed aldol-type cyclisations in N-substituted-2-nitroanilines. In particular, N-benzyl-2-nitroanilines [e.g. (47; R = Ar)] with a wide variety of substituents on both benzene rings have been cyclised to the

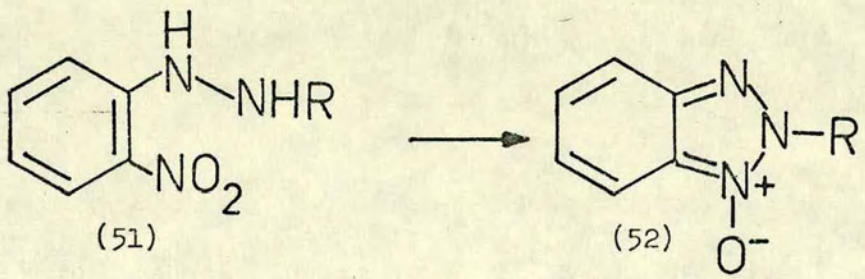


(47) (48)

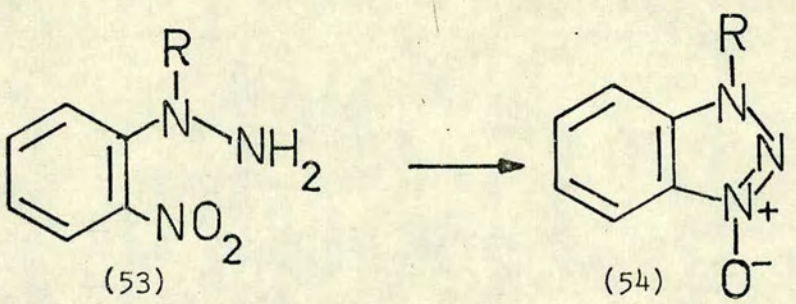
corresponding N-hydroxybenzimidazoles (48; R = Ar)[36,37] and N-thiazolylmethyl-2-nitroanilines (47; R = 2- or 4-thiazolyl) have



(49) (50)



(51) (52)



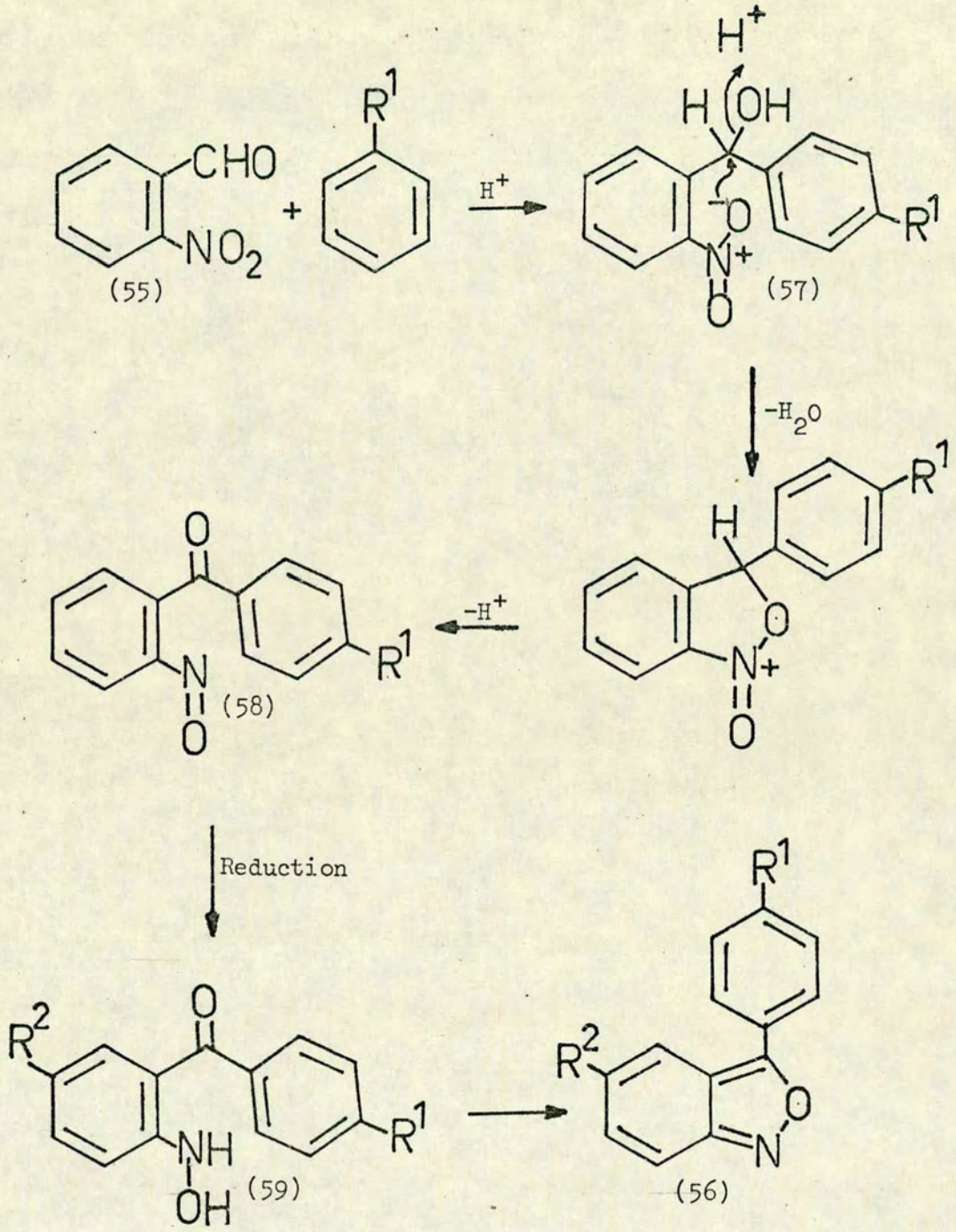
(53) (54)

been cyclised to the corresponding N-hydroxybenzimidazoles (48; R = 2- or 4-thiazolyl).[38]

By far the most important method available for the synthesis of benzotriazole N-oxides is the base-catalysed cyclisation of 2-nitrophenylhydrazine derivatives. The base-catalysed transformation of 2-nitrophenylhydrazine (49) was discovered by Freund[39] and Willgerodt[40] and the product was later identified by Nietzki and Braunschweig[41] as 1-hydroxybenzotriazole (50) which is tautomeric with benzotriazole 1-oxide (52 or 54; R = H). Since then, a large number of N-hydroxybenzotriazoles with a variety of substituents in the benzene ring have been synthesised by this method. Base-catalysed cyclisation of 2-substituted-1-(2'-nitrophenyl)hydrazines (51) affords 2-substituted benzotriazole 1-oxides (52)[42,43] and similar cyclisation of 1-substituted-1-(2'-nitrophenyl)hydrazines (53) affords 3-substituted benzotriazole 1-oxides (54).[44]

(ii) Cyclisations of Ortho-Nitrobenzene Derivatives involving Intramolecular Redox Processes.

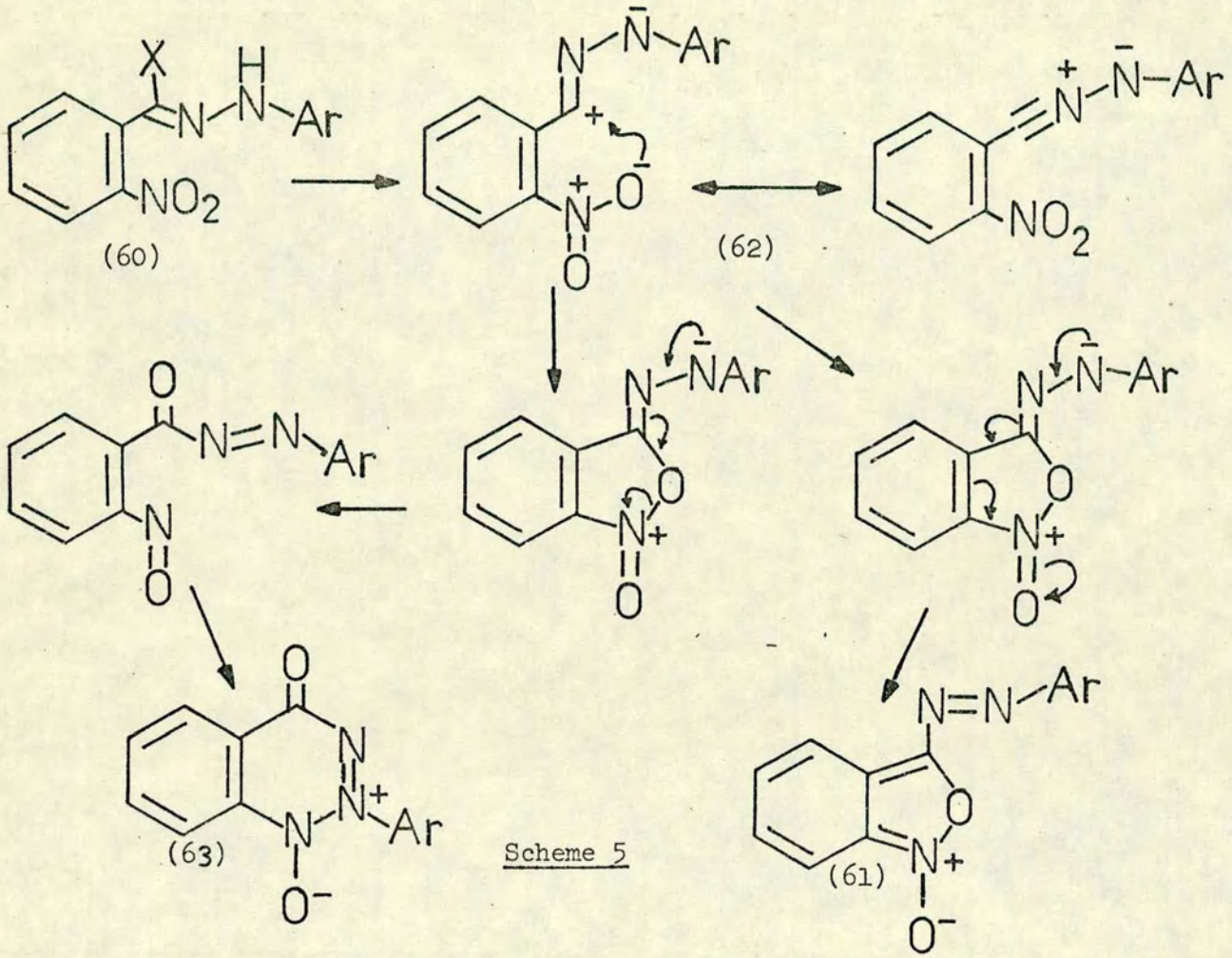
Many examples of acid-catalysed cyclisations of 2-nitrobenzene derivatives have been reported. In most, but not all, of these reactions the mechanism of cyclisation involves an intramolecular redox reaction whereby an oxygen atom is transferred from the nitro group to the ortho-side chain. The earliest examples of such cyclisations are to be found in acid-catalysed reactions which lead to the formation of anthranils. Zincke and his co-workers reacted 2-nitrobenzaldehyde (55) with phenol in acetic acid saturated with hydrogen chloride[45] and with aniline in concentrated hydrochloric acid[46] and obtained the corresponding 3-arylanthranils (56; R^1 = OH or NH_2, R^2 = Cl). Since then a number of 3-arylanthranils (56)



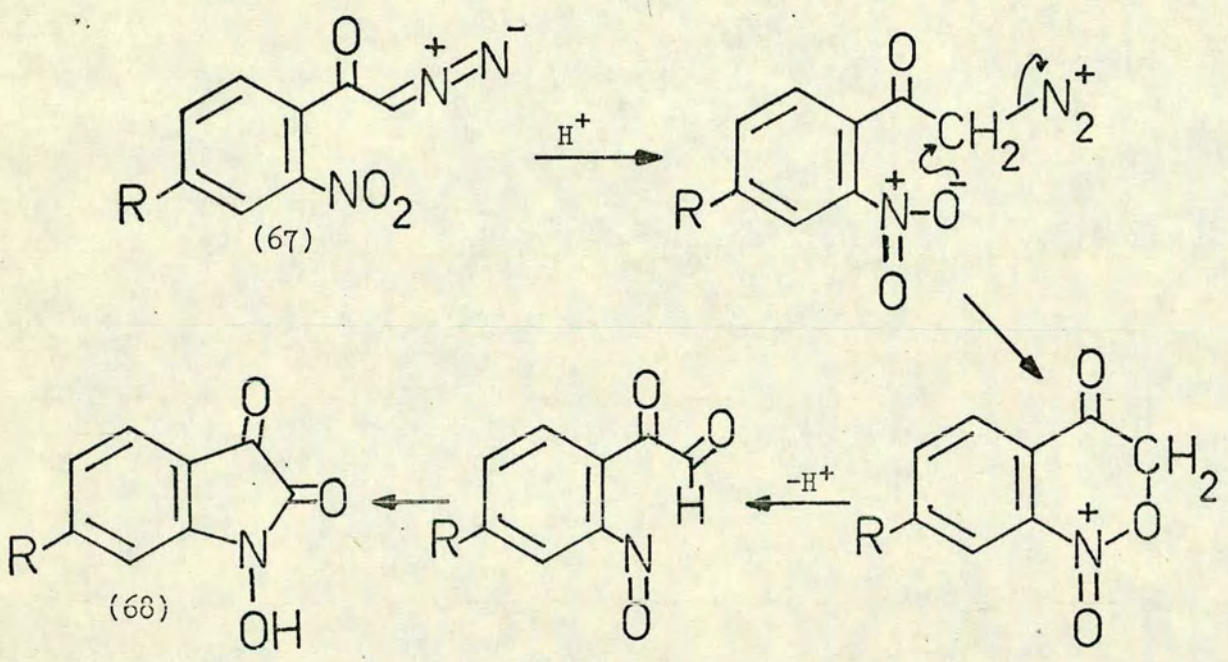
Scheme 4

have been prepared by acid-catalysed reaction of 2-nitrobenzaldehyde with substituted benzene derivatives, using, as catalyst, concentrated sulphuric acid,[47] hydrogen halides,[48] aqueous hydrochloric acid[46] or zinc chloride[49]. The probable mechanism of these reactions is generalised by the formation of 3-phenylanthranil (56; $R^1 = R^2 = H$) from 2-nitrobenzhydrol (57; $R^1 = H$) by the action of thionyl chloride[50] or concentrated sulphuric acid.[51] Evidence for the involvement of an intramolecular redox process [(57)→(58)] is provided by the formation of 2-nitrosobenzophenone (58; $R^1 = H$) from 2-nitrobenzhydrol (57; $R^1 = H$) on treatment with tosyl chloride in pyridine or 98% formic acid.[50] In the case of the hydrogen chloride reactions,[45,48] the reduction step [(58)→(59)] is effected by entry of chloride ion and the products are 5-chloro-3-arylanthranils (56; $R^2 = Cl$). Halogen is not incorporated into the product when hydrogen chloride in the presence of quinol or hydrogen bromide is used as catalyst.[48] In the other cases, the reduction step [(58)→(59)] is effected by unreacted benzhydrol (57) which is oxidised to 2-nitrobenzophenone thus accounting for the formation of this compound as a by-product.

Bromination in the presence of sodium acetate of 2-nitrobenzaldehyde arylhydrazones (60; X = H)[52,53] or reaction of the corresponding hydrazidic halides (60; X = Cl, Br) with ammonia in benzene[52,53] gives products which have been formulated as 3-arylazoanthranil 1-oxides (61) on the basis of mechanistic arguments (Scheme 5).[54] A recent report,[55] which includes extensions of the reaction, also contains a kinetic study which lends support to the intermediacy of nitrile-imines (62) in these cyclisations. The same products are obtained by oxidation of the arylhydrazones

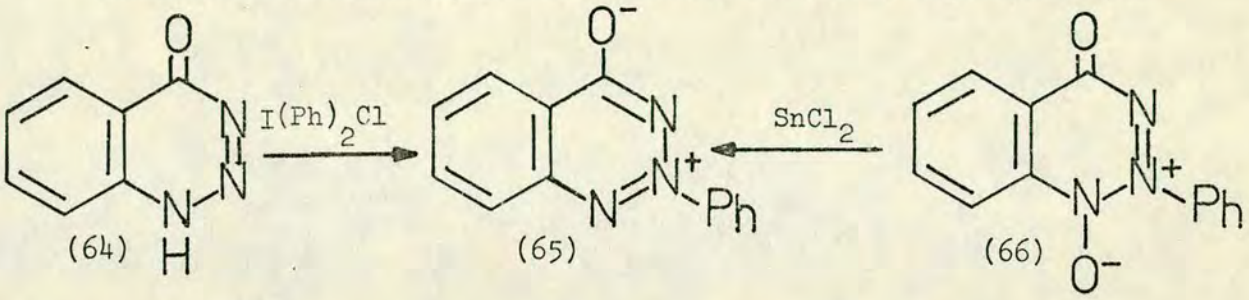


Scheme 5



(60; X = H) with lead tetraacetate.[56] More recently, however, Kerber has reformulated the products as 2-arylbenzotriazin-4-one 1-oxides (63) (Scheme 5) on the basis of spectral arguments.[57] This latter structural assignment has been proved correct by degradation and synthesis.[58]

Phenylation of benzo-1,2,3-triazin-4-one (64) with diphenyliodonium



(64) (65) (66)

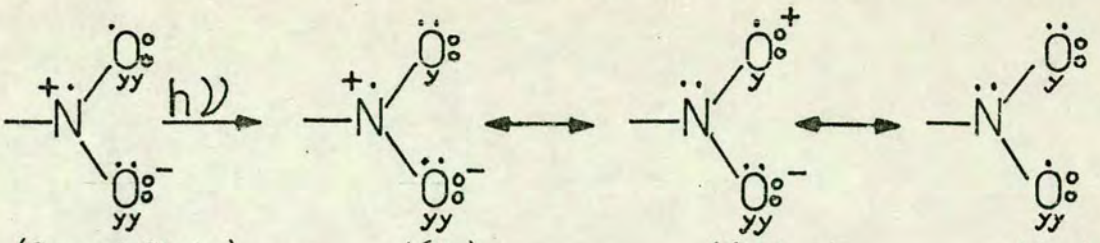
chloride affords the 2-phenylbenzo-1,2,3-triazinium betaine (65) which is identical to the product obtained on reduction with stannous chloride of the supposed 2-phenylbenzo-1,2,3-triazin-4-one 1-oxide (66).

Acid-catalysed cyclisation of 2-nitrobenzoyldiazomethanes (67) gives the corresponding N-hydroxyisatins (68)[59,60] which are not accessible by other means. The mechanism proposed by Moore and Ahlstrom[61] involves an intramolecular oxygen transfer as shown and labelling experiments have been used to exclude a mechanism involving a Wolff rearrangement.[62]

(iii) Photochemical Cyclisations of Ortho-Substituted Nitrobenzene Derivatives.

The photochemistry of nitro compounds[63] bears certain similarities to that of carbonyl compounds but the photochemical reactivity of the nitro group has not been so extensively studied as that of the carbonyl group. Studies of the emission spectra of certain aromatic nitro compounds suggest that the lowest excited state is an n,π^* triplet state.[64] However, irradiation of the nitro group appears to cause an $n\rightarrow\pi^*$ transition giving the first

excited singlet state which can be represented using the Zimmerman

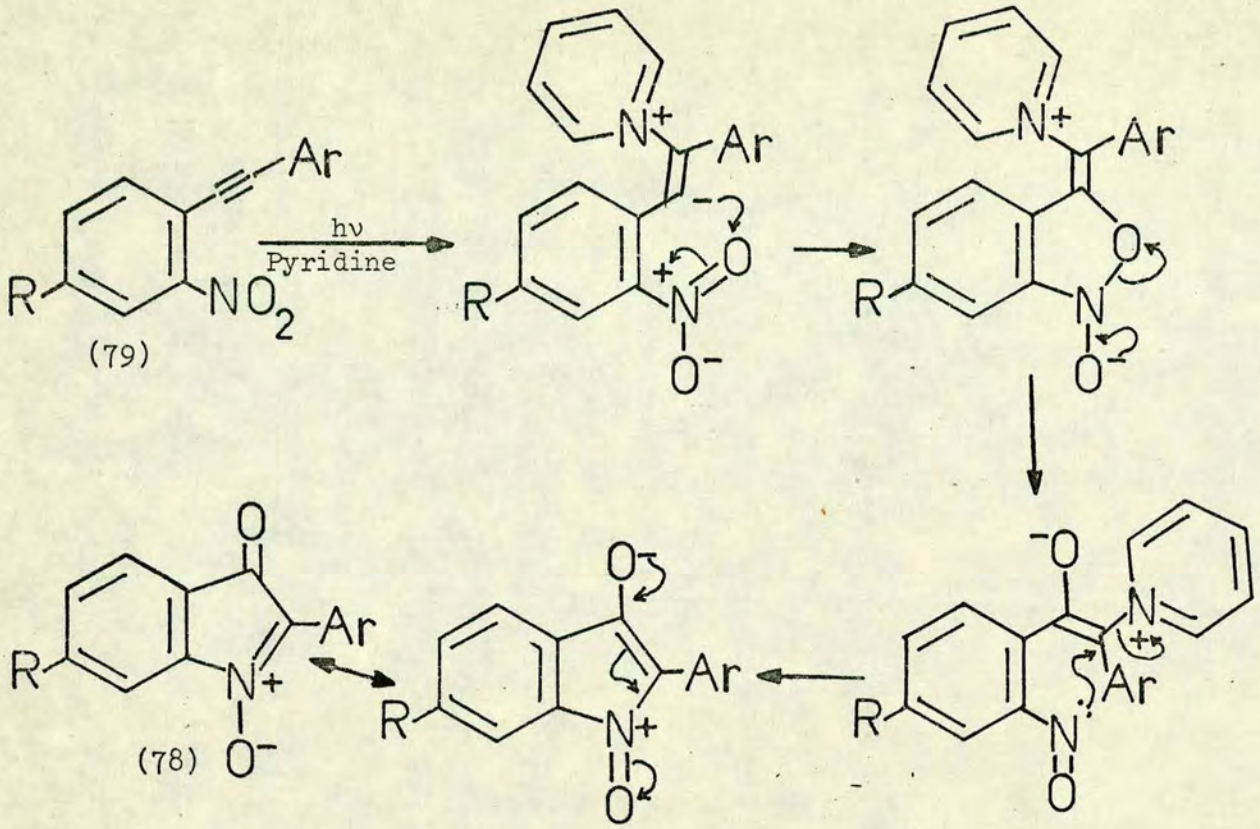


(Ground State) (69a) (69b) (69c)

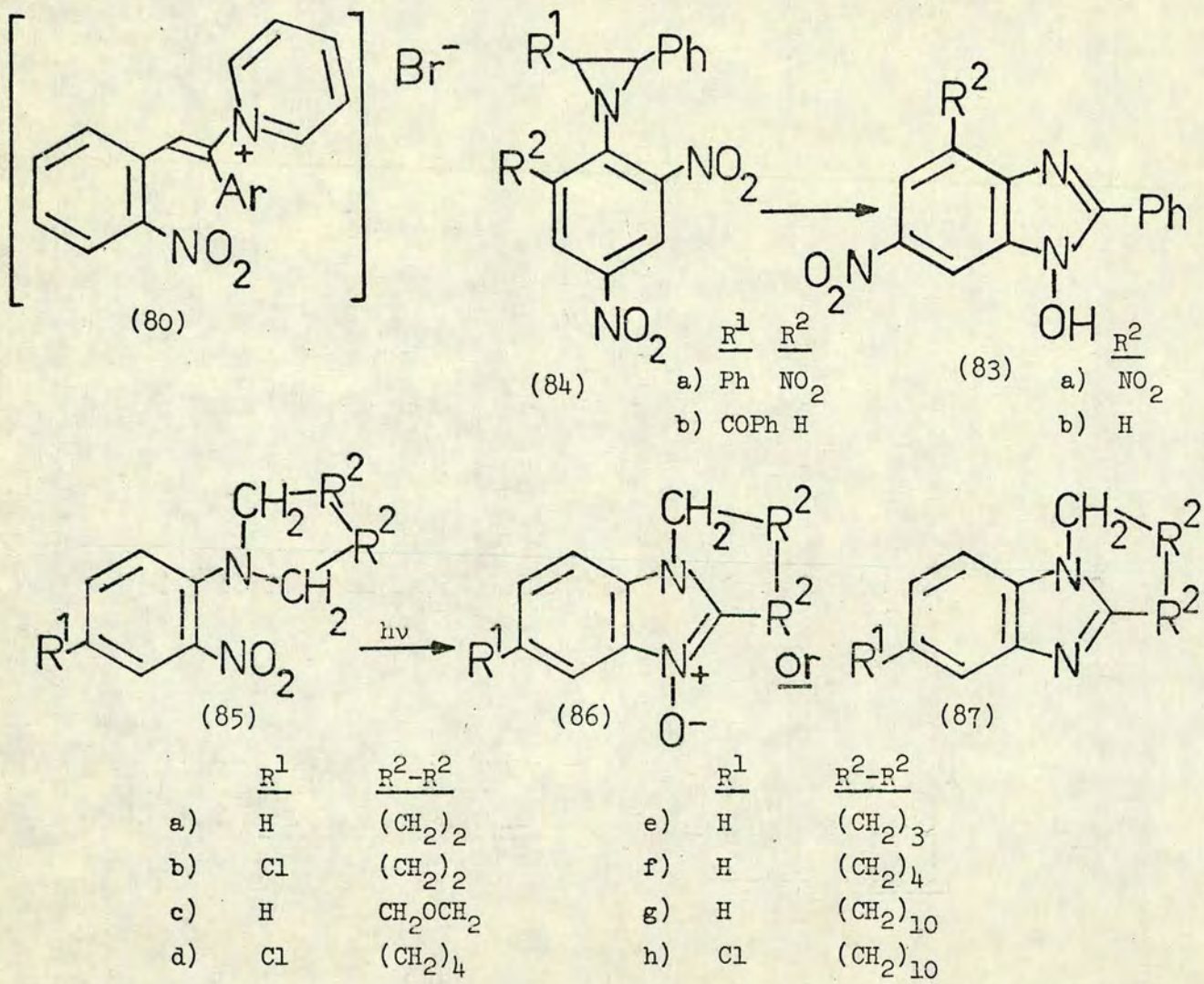
(· = π electron, o = sp electron, y = p_y electron)

notation[65] by the structures (69 a-c). The contribution of structure (69c) to the excited state of the nitro group suggests the possibility of the photoinduced addition of the nitro group to a double bond. This is the initial step for the mechanism proposed by Splitter and Calvin to rationalise the formation of isatogens (70) in the photolysis of 2-nitrostilbenes (71) (Scheme 6).[66] The formation of the isatogen (70; Ar = p-Me_2N-C_6H_4), the indoxyl (72; Ar = p-NMe_2-C_6H_4), the anthranil (73) and 4-dimethylaminobenzaldehyde (74; Ar = p-NMe_2-C_6H_4) are all conveniently explained by the postulation of the intermediate cycloadduct (75). Analogy for the intermediate (76) is provided by the reported[67] formation of the N-oxide (77) on irradiation of 2-nitrocinnamic acid.

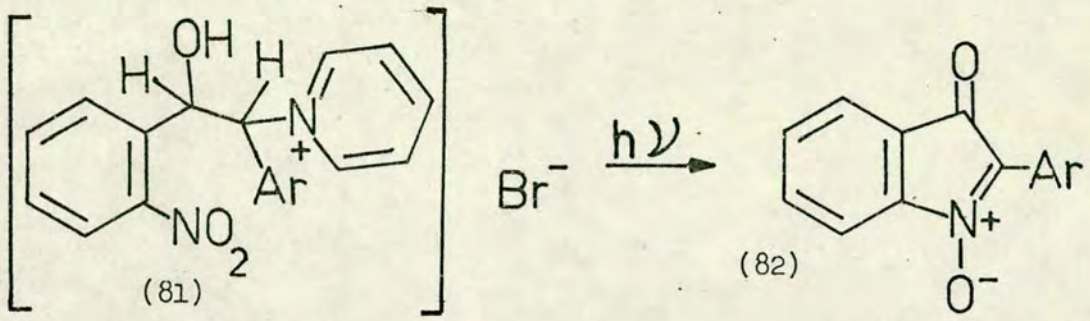
Photochemical methods are very useful in the synthesis of 2-arylisatogens. Photolysis of 2-nitrostilbene dichlorides, 2-nitromonochlorostilbenes and 2-nitrotolans in pyridine to give 2-arylisatogens was first reported by Pfeiffer[68] and further extended by Ruggli and his co-workers.[69-72] Huisgen[73] has proposed the following mechanism (Scheme 7) to explain the formation of isatogens (78) from 2-nitrotolans (79). In this mechanism it is proposed that the only step requiring the action of light is the addition of pyridine to the acetylene.



Scheme 7



Possible support for this contention is provided by the ready base-catalysed formation of isatogens from pyridinium salts of the type (80), whereas salts of the type (81) are stable to these conditions.[74]

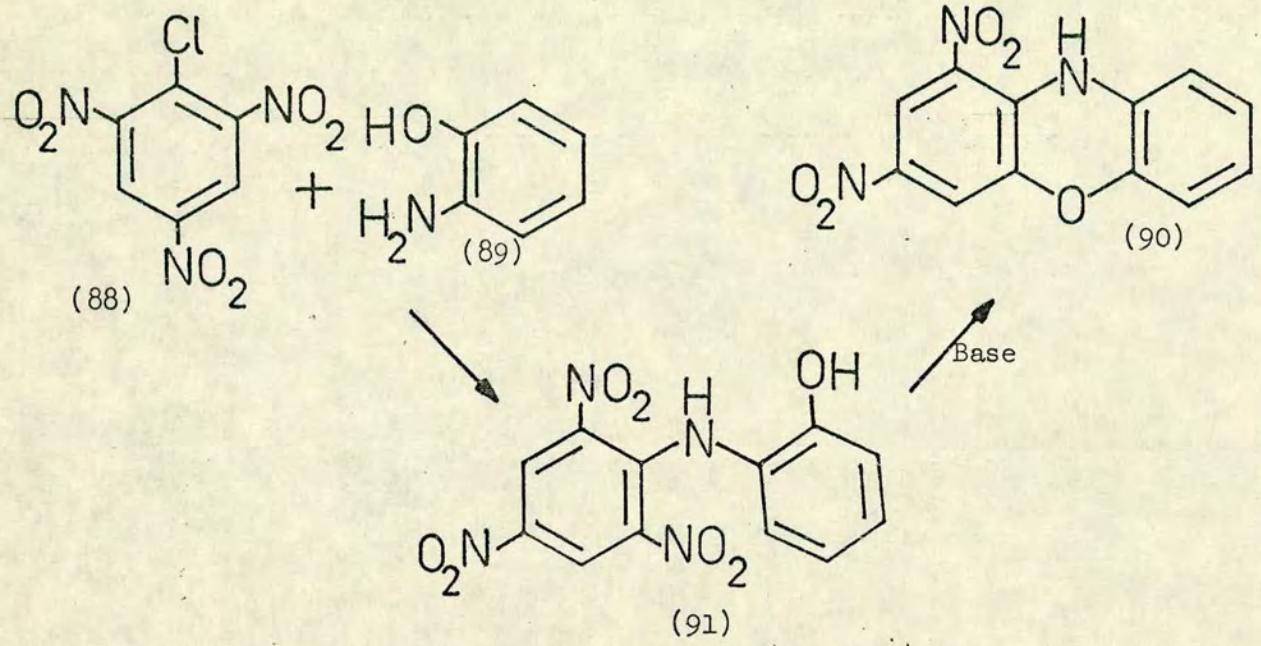


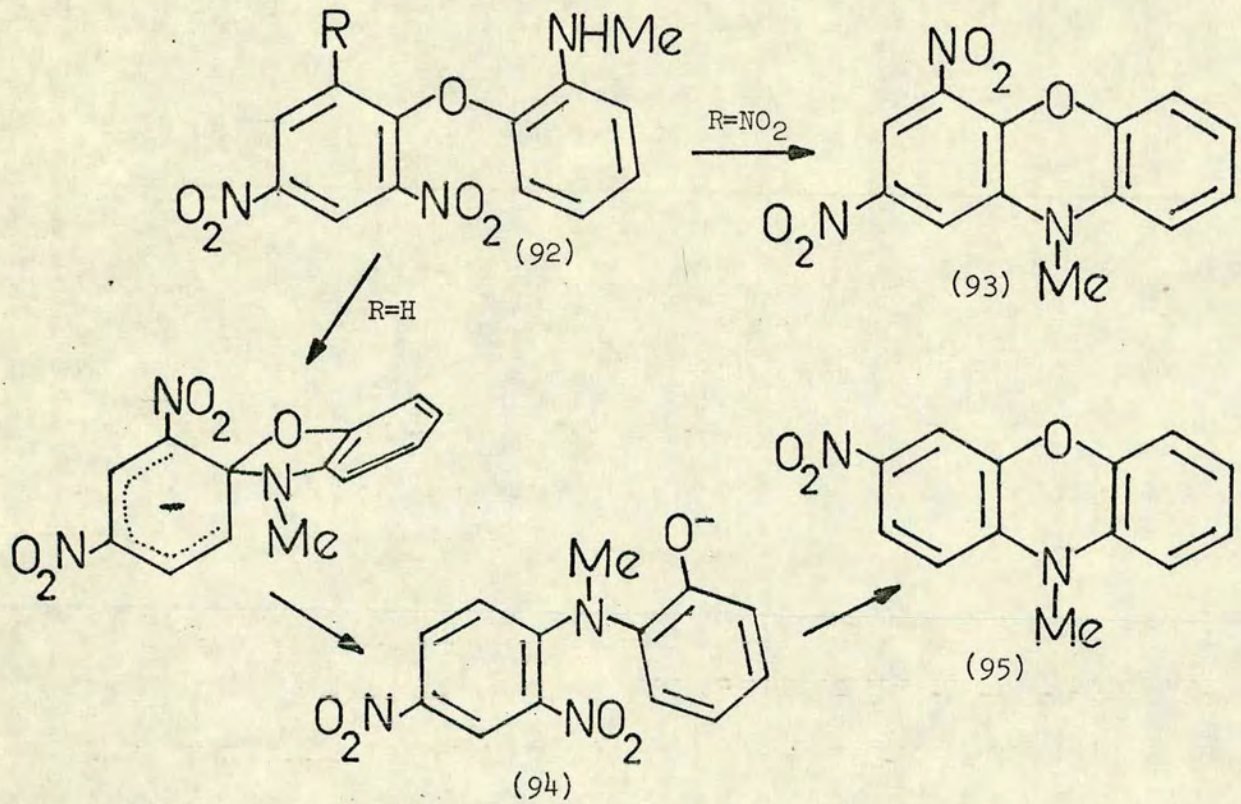
(81) (82)

The salts (81), however, give good yields of the corresponding isatogens (82) on irradiation.[75]

N-Hydroxybenzimidazoles (83 a and b) are formed in high yield by irradiation in ethanol of the N-(2-nitrophenyl)aziridines (84 a and b).[76] A related photochemical synthesis of benzimidazoles or their N-oxides has been developed by Suschitzky and his co-workers.[77] Irradiation of solutions of the N,N-disubstituted 2-nitroanilines (85 a-d) in aqueous methanolic hydrochloric acid gives the benzimidazole N-oxides (86 a-d) whereas irradiation of the N,N-disubstituted 2-nitroanilines (85 e-h) gave the benzimidazoles (87 e-h). There appear to be two different mechanisms operating in these reactions since the concomitant formation of (86) and (87) is not observed. The factors favouring the formation of N-oxides seem to be low basicity in the amine, the presence of small N-substituents and also the presence of an electron-withdrawing group (e.g. Cl) in the aromatic ring although the large ring chloro compound (85 h) gives only the benzimidazole (87 h).

(iv) Cyclisations of Ortho-substituted Nitrobenzene Derivatives involving the Intramolecular Nucleophilic Displacement of the Nitro Group


Cl
O_2N
NO_2
NO_2
HO
H_2N
(88)
(89)
NO_2
H
N
O_2N
O
(90)
Base
NO_2
H
N
OH
O_2N
NO_2
(91)


R
NHMe
O
O_2N
NO_2
(92)
$R=NO_2$
NO_2
O
O_2N
N
Me
(93)
R=H
NO_2
O
O_2N
N
Me
Me
N
O⁻
O_2N
NO_2
(94)
O_2N
O
N
Me
(95)

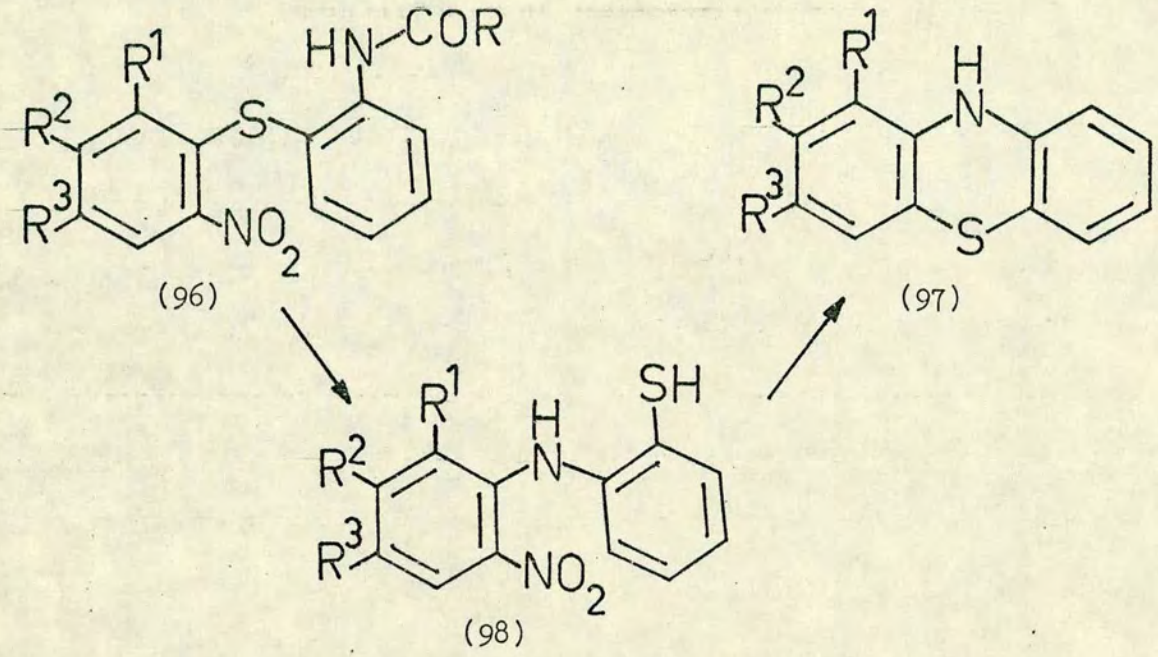
Not only is the nitro group capable of activating the ortho- and para-positions of the benzene ring to nucleophilic substitution,[78] but under suitable conditions it can itself undergo displacement by a nucleophile. Thus, hydrolysis and methanolysis of o- and p-dinitrobenzenes give the corresponding nitrophenols and nitroanisoles respectively,[79] while 2- and 4-nitrobenzonitriles under similar conditions give the corresponding cyanophenols and cyanoanisoles respectively.[80]

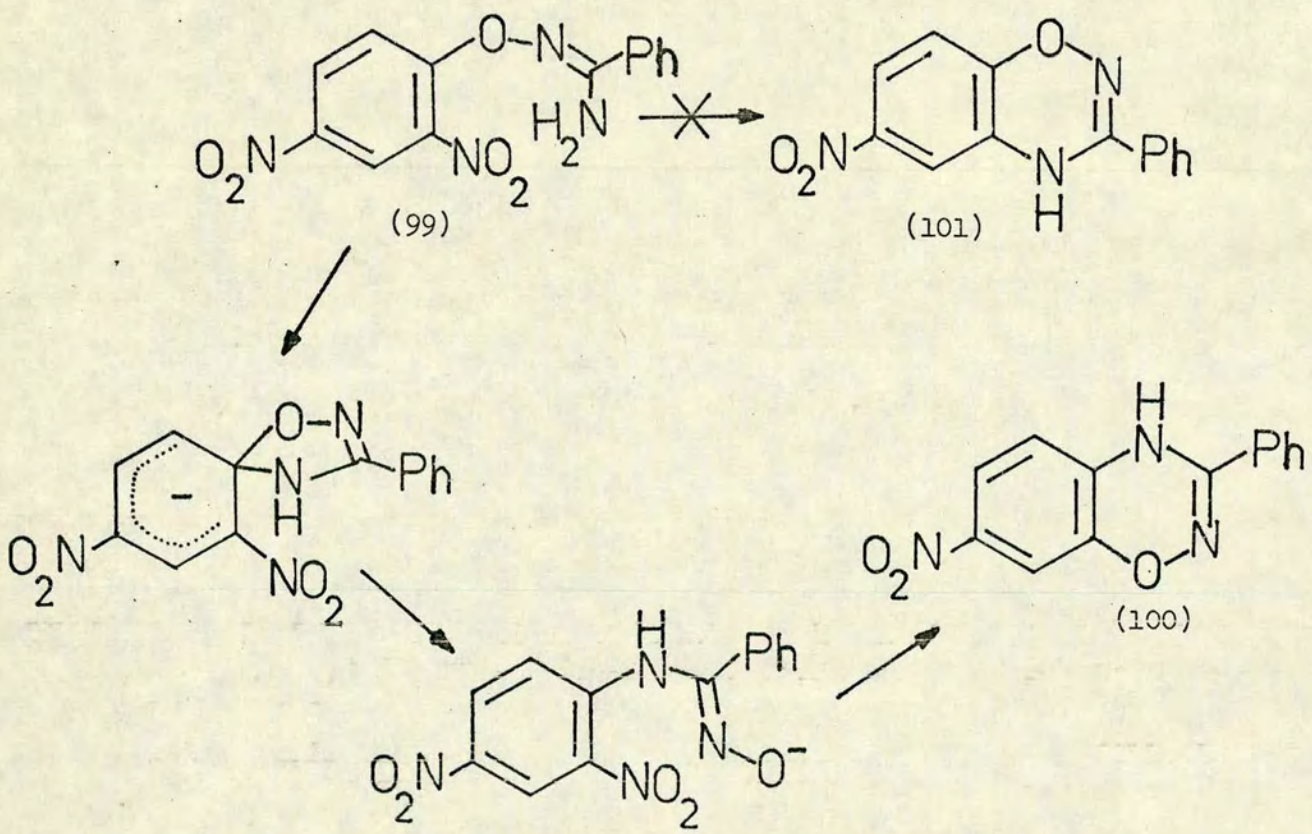
The first report of an intramolecular nucleophilic displacement of a nitro group by an ortho-side chain was by Turpin[81] who, in a study of the base-catalysed condensation of picryl chloride (88) with 2-aminophenol (89), obtained the dinitrophenoxazine (90). This product is readily explained in terms of the intramolecular displacement of an ortho-nitro group by the hydroxyl group in the diphenylamine intermediate (91).

A similar synthesis of phenoxazines involves the base-catalysed cyclisation of 2-amino-2'-nitrodiaryl ethers (92). When the trinitrodiphenyl ether (92; R = NO_2) undergoes cyclisation, the ortho-nitro group is displaced by the amino group to give the phenoxazine (93).[82] However, cyclisation of the dinitrophenyl ether (92; R = H) results in Smiles rearrangment to give the phenolate anion (94) which undergoes cyclisation to give the phenoxazine (95).[83]

The similar cyclisations of 2-acylamino-2'-nitrodiaryl sulphides (96) to phenothiazines (97) have been extensively studied by Smiles and his co-workers.[84-86] They showed that cyclisation was always preceded by rearrangement to the diphenylamine (98) followed by displacement of the nitro group by thiophenoxide ion.

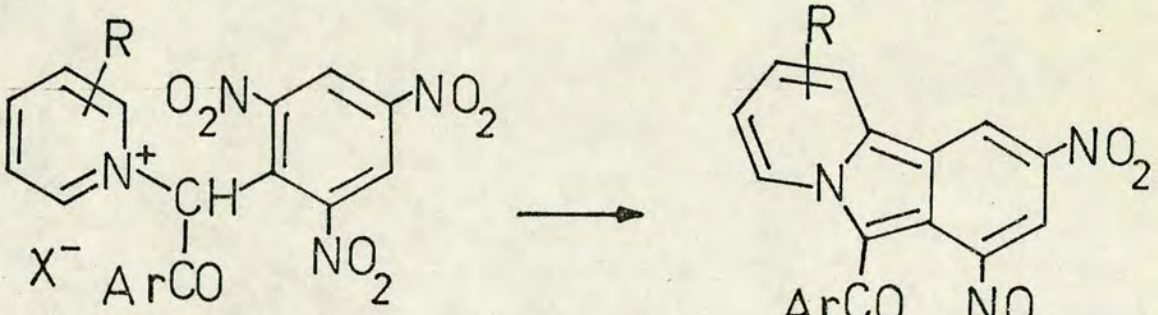
The base-catalysed cyclisation of the amidoxime (99) reported by Werner and Herberger[87] has recently been shown by independent synthesis[88] to afford 7-nitro-3-phenylbenz-1,2,4-oxadiazine (100) and not the 6-nitro


HN-COR
R1
R2
R3
S
NO2
(96)
H
N
S
(97)
SH
(98)


O-N
Ph
H2N
O2N
NO2
(99)
(101)
(100)

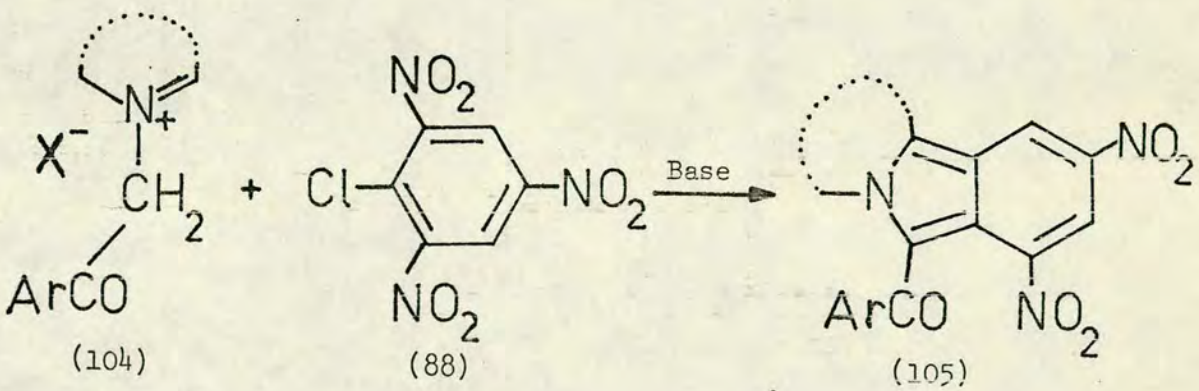
isomer (101) as originally reported. Again, Smiles rearrangement takes place prior to cyclisation in this reaction.

Whereas cyclisation involving the intramolecular displacement of aromatic nitro groups by oxygen, sulphur and nitrogen nucleophiles are well known processes, similar reactions involving carbon nucleophiles are relatively rare. Krohnke and his co-workers[89-91] have synthesised a variety of interesting heterocycles containing a bridge-head nitrogen atom by reactions involving the displacement of a nitro group by a carbanion. Thus, treatment of the pyridinium salts (102) with piperidine gives the benzoindolizines (103) in high yield.[89] This type of cyclisation has been extended to N-phenacyl

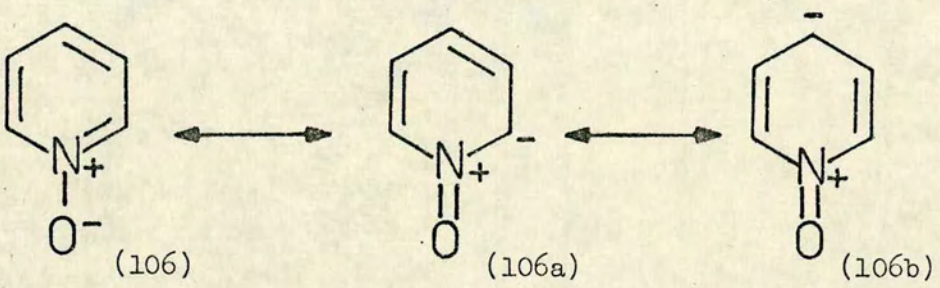


(102) (103)

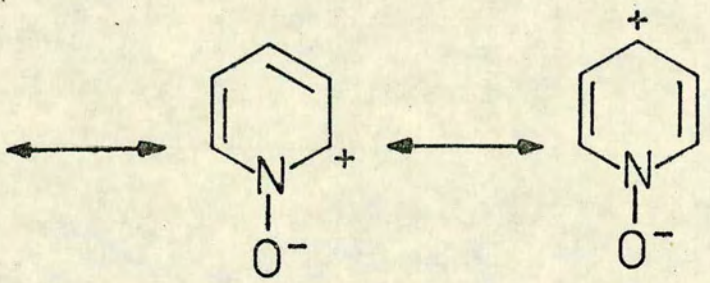
salts of the type (104) which, with picryl chloride (88) in the presence of base, give the polycyclic isoindoles (105) where the bridge-head nitrogen atom is contained in a quinoline, isoquinoline, benzimidazole or thiazole ring.[90] Other similar cyclisations,



(104) (88) (105)



(106) (106a) (106b)



(106c) (106d)

developed by the same workers[91] have resulted in the formation of a range of interesting fused heterocycles.

PART 2

Nucleophilic Substitution Reactions of Heteroaromatic N-Oxides.

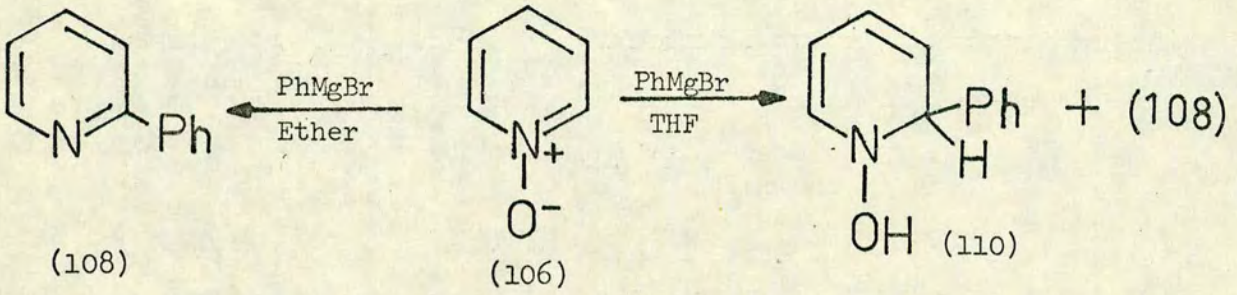
The importance and versatility of ortho-nitrobenzene derivatives as starting materials for the synthesis of a wide variety of heterocycles, particularly N-oxygenated benzazaheterocycles, has already been discussed. N-Oxygenated heterocycles are of particular interest due to their enhanced reactivity in comparison with the parent heterocycles.

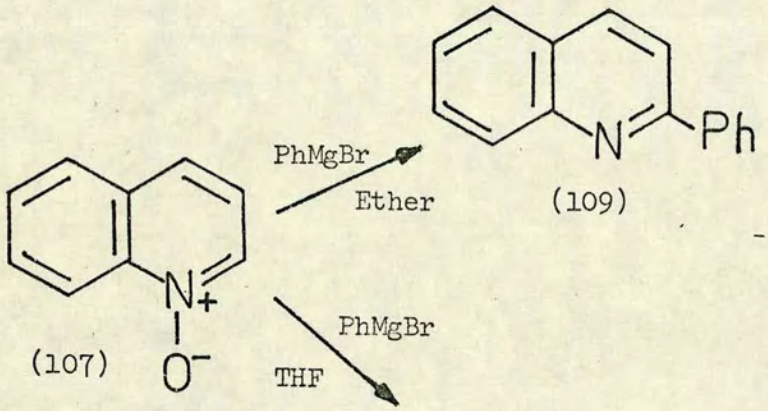
The work of Meisenheimer[92] on the direct N-oxidation of heterocyclic compounds provided the initial stimulus to the study of the chemistry of heterocyclic N-oxides but the first major advances in the field came with the measurement by Linton[93] of the dipole moment of pyridine 1-oxide (106) and the recognition by Ochiai[94] of the implications of Linton's findings. The dipole moment of pyridine 1-oxide (106) was found to be significantly less than the predicted value, suggesting a certain degree of back-polarisation which can be explained in terms of the resonance forms (106a) and (106b). This led Ochiai[94] to predict and subsequently to establish experimentally the ability of pyridine 1-oxide (106) to undergo electrophilic substitution at the 2- and 4-positions of the ring. The same conclusions were reached independently by den Hertog.[95] The importance of the resonance forms (106c) and (106d) has also been recognised[95] and accounts for the reactivity of pyridine 1-oxide (106) towards nucleophilic substitution in the 2- and 4-positions. It is this

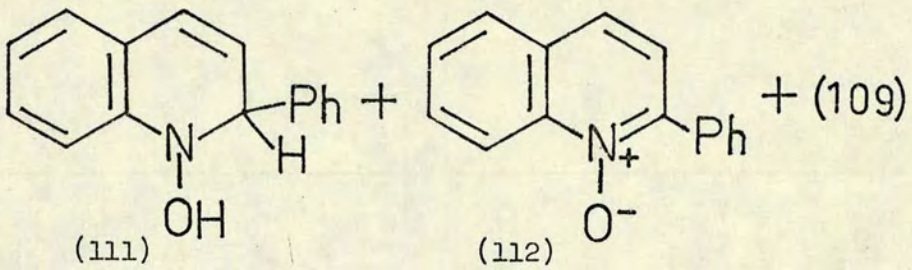
remarkable ability of the N-oxide group to polarise a heteroaromatic ring in both possible electronic senses which has promoted the widespread interest in the synthesis of N-oxides and in the study of their reactivity. N-Oxides have been the subject of two text-books[97,98] and numerous reviews.[98a] The reactivity of N-oxides can be broadly classified under four headings, namely (i) electrophilic reactions at the oxygen atom of the N-oxide group, (ii) electrophilic substitution in the ring, (iii) nucleophilic substitution in the ring (often involving initial electrophilic attack at the oxygen atom of the N-oxide group), and (iv) activation of exocyclic substituents by the N-oxide group. In the following survey attention is centred on reactions of heteroaromatic N-oxides resulting in nucleophilic substitution and where relevant the activating effect of the N-oxide group on exocyclic substituents. Reactions involving electrophilic substitution are outside the scope of the survey and are excluded from the discussion which follows.

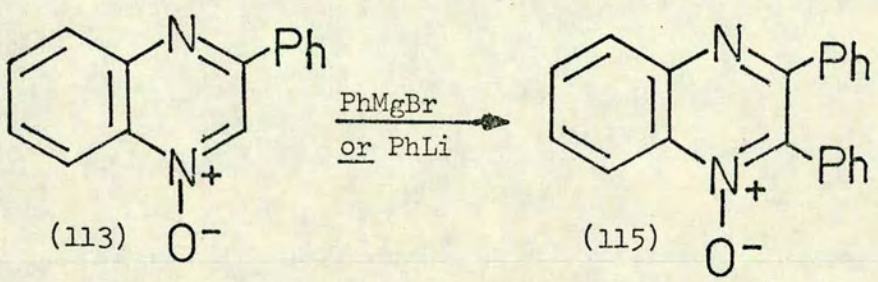
A. Reaction with Organometallic Reagents.

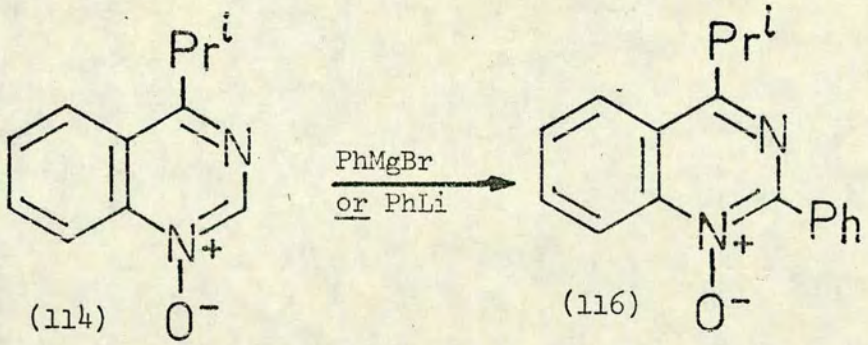
As discussed before, polarisation by the N-oxide group promotes nucleophilic attack at the α- or γ-positions of the ring in hetero-aromatic N-oxides. As a result, a large number of nucleophilic substitution reactions of heteroaromatic N-oxides have been investigated. However, only organometallic reagents are powerful enough nucleophiles to effect direct nucleophilic substitution in heteroaromatic N-oxides. The reactions of pyridine 1-oxide (106) and quinoline 1-oxide (107) with Grignard reagents have been well investigated. With ethereal phenylmagnesium bromide, the products are 2-phenylpyridine (108)[99,100] and 2-phenylquinoline (109)[99] respectively. However, in tetrahydrofuran as solvent, pyridine


PhMgBr
Ether
PhMgBr
THF
Ph
+ (108)
(108)
(106)
(110)


PhMgBr
Ether
(109)
(107)
PhMgBr
THF

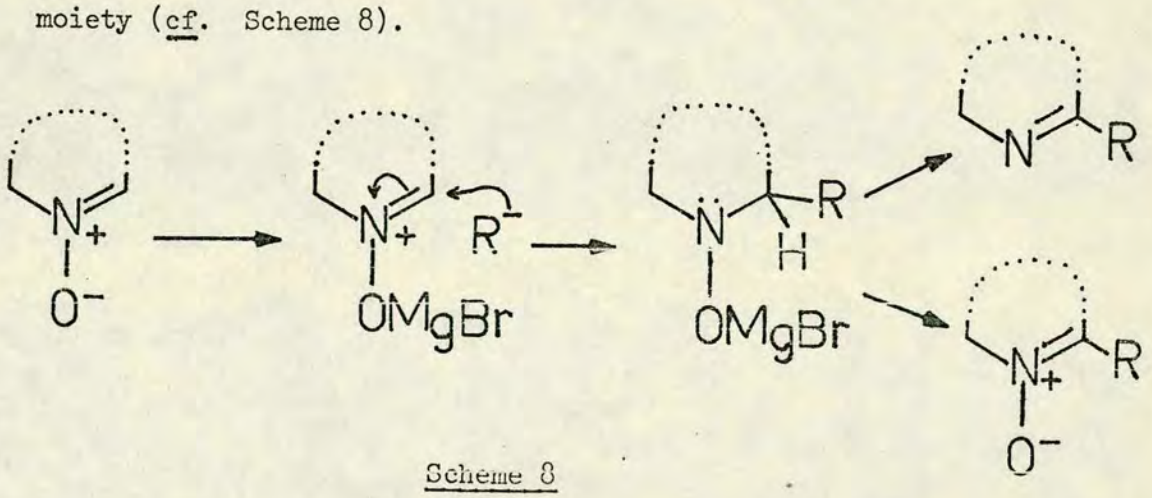

+
+ (109)
(111)
(112)


PhMgBr
or PhLi
(113)
(115)

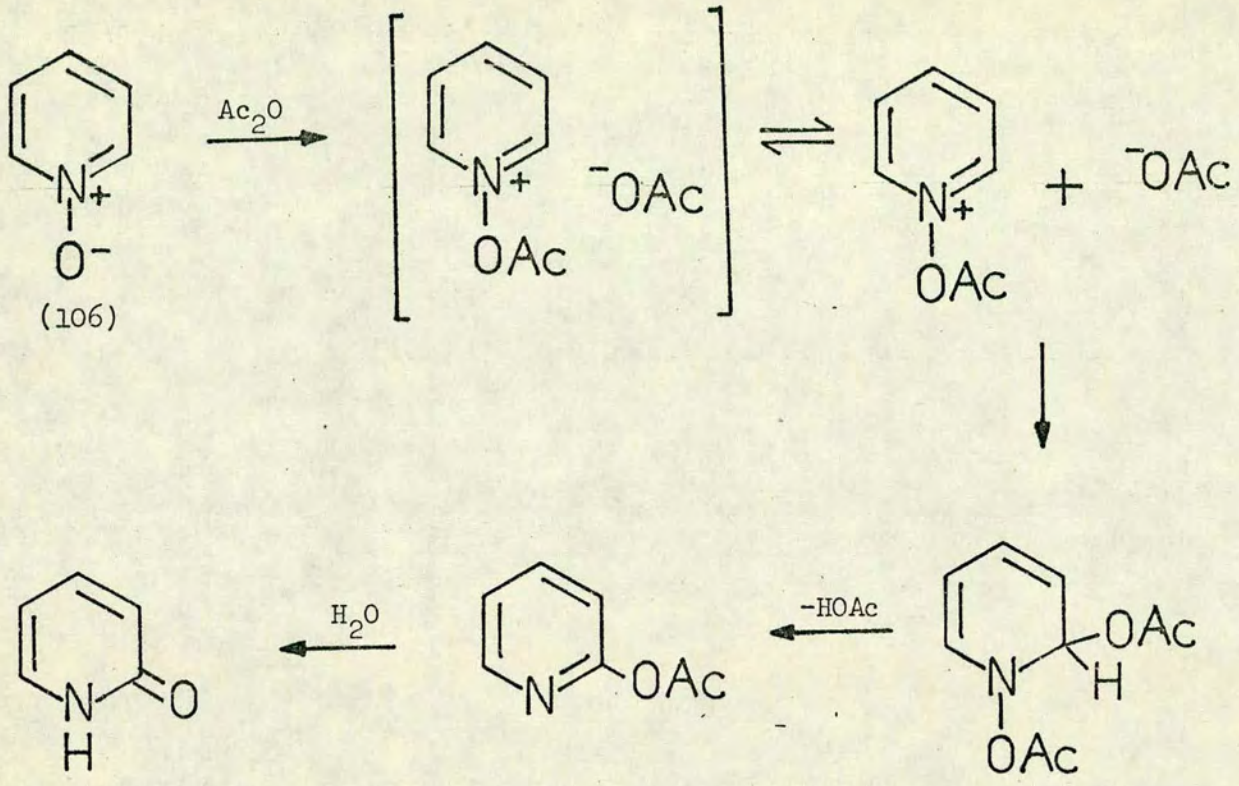

PhMgBr
or PhLi
(114)
(116)

1-oxide (106) reacts with phenylmagnesium bromide to give 1-hydroxy-2-phenyl-1,2-dihydropyridine (110) as the main product in addition to the expected product (108) which may be obtained from (110) by heating.[101] The reaction of quinoline 1-oxide (107) with phenylmagnesium bromide in the presence of tetrahydrofuran is similar and gives the adduct (111), 2-phenylquinoline (109) and also 2-phenylquinoline 1-oxide (112).[101] The latter product is presumably derived from the adduct (111) by oxidation since (111) is converted into (112) in the presence of air.[101] Retention of the N-oxide group is not uncommon in reactions of heteroaromatic N-oxides with organometallic reagents. Thus, 3-phenylquinoxaline 1-oxide (113)[102] and 4-isopropylquinazoline 1-oxide (114)[103] react with either phenylmagnesium bromide or phenyllithium to give 2,3-diphenylquinoxaline 1-oxide (115) and 4-isopropyl-2-phenylquinazoline 1-oxide (116) respectively. Only traces of the reduced heterocycles are formed. Also, sodium acetylide[104] and sodium phenylacetylide[105] react with pyridine 1-oxide (106) to give the corresponding 2-alkynylpyridine 1-oxides.

Ochiai[105] has suggested that the reactions of heteroaromatic N-oxides with Grignard reagents involves preliminary co-ordination of the metal at the N-oxide oxygen atom thereby activating the α-position to subsequent nucleophilic attack by the carbanion moiety (cf. Scheme 8).

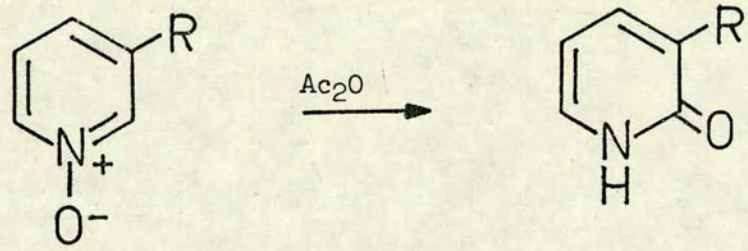


Scheme 8



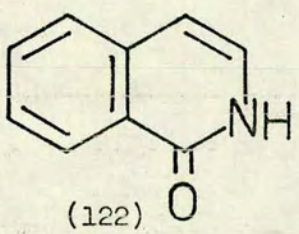
(106)

Scheme 9



(119)

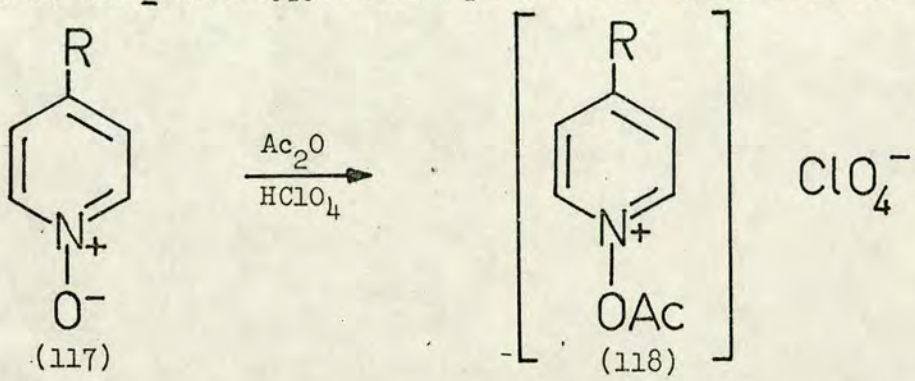
(120)



(122)

B. Reaction with Acid Anhydrides.

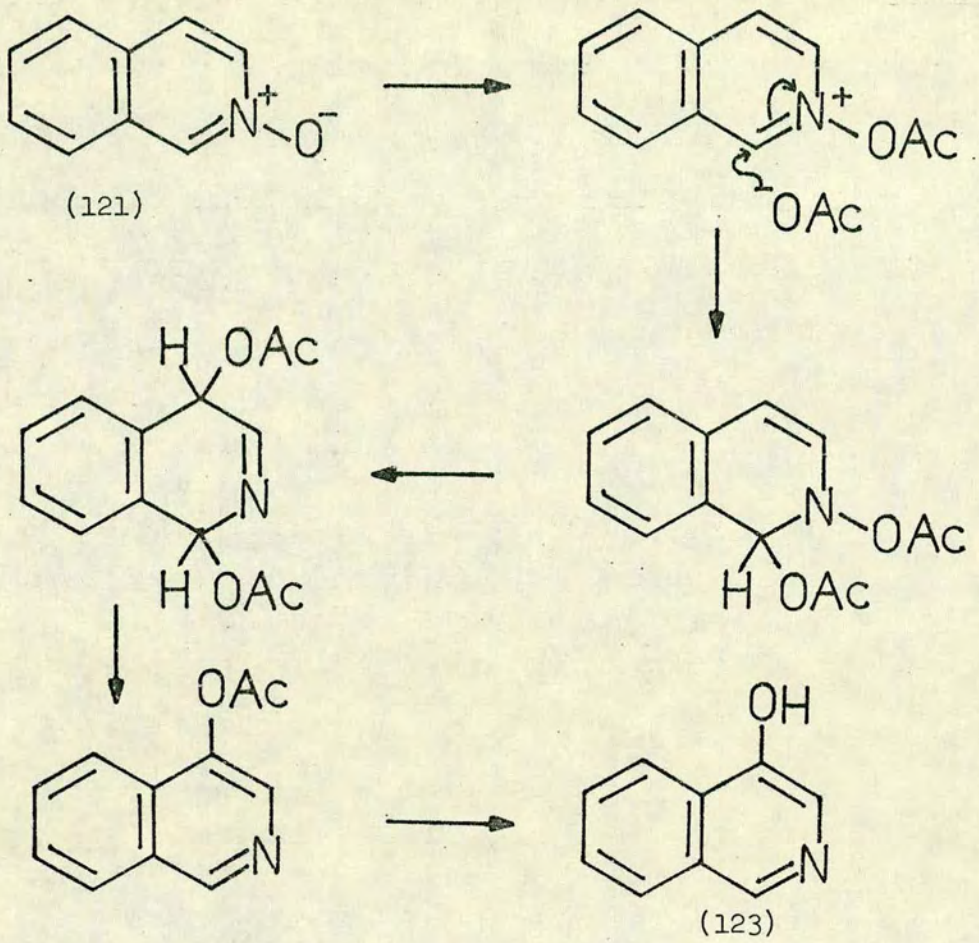
The reactions of heteroaromatic N-oxides with acetic anhydride have been extensively studied. The first step in such reactions is believed to be acylation at the N-oxide oxygen atom to give an N-acetoxy quaternary salt which is susceptible to further reaction with nucleophiles. Evidence for this postulate is provided by the isolation of the N-acetoxypyridinium perchlorates (118) from the



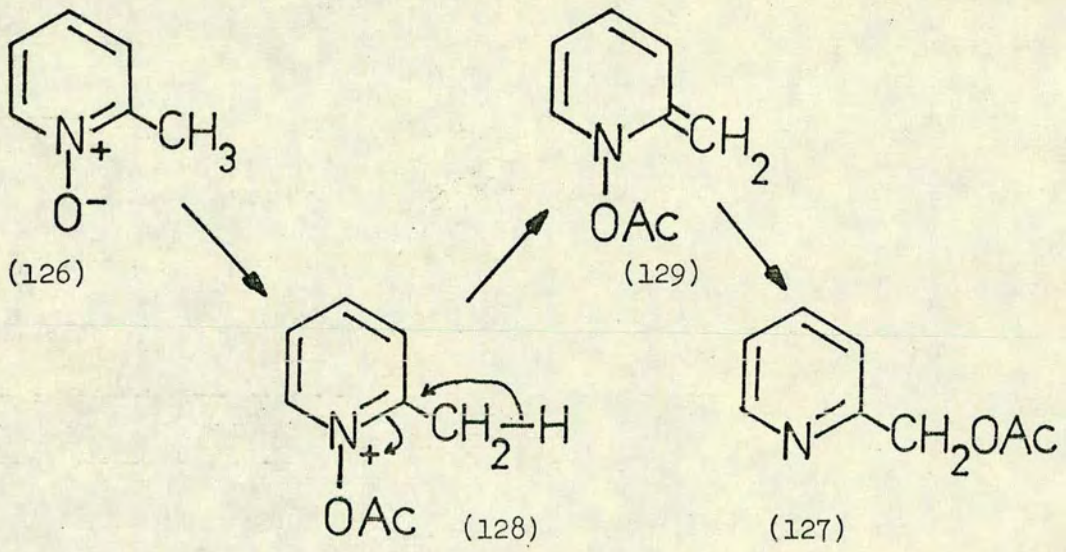
(117) (118)

reaction of the pyridine N-oxides (117) with acetic anhydride in the presence of perchloric acid.[107] The use of perchloric acid has also enabled N-acetoxy perchlorates to be isolated in the quinoline[108] and quinoxaline series.[109]

The detailed mechanism of the reaction of pyridine 1-oxide (106) with acetic anhydride[110] has been the subject of a great deal of controversy. Oae and his co-workers[111,112] have used isotopic labelling techniques to demonstrate that an intermolecular process is involved. The absence of gaseous products[113] suggests that free radicals are not involved and an ionic mechanism (Scheme 9) has been postulated on the basis of kinetic studies.[113] Further evidence for the ionic nature of the reaction is provided by the almost exclusive formation of 3-substituted pyridin-2-ones (120) in the reaction of acetic anhydride with pyridine 1-oxides (119) containing an electron-withdrawing group in the 3-position (e.g. nitro, halogeno or ethoxycarbonyl).[114] Cohen and Deets[115] have

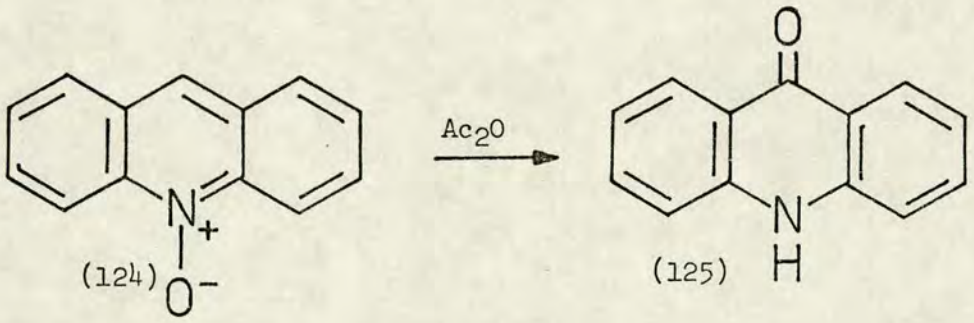


Scheme 10



also provided evidence for an ionic pathway by performing the reaction of pyridine 1-oxide (106) with acetic anhydride in anisole or benzonitrile as co-solvent. Studies on the product distributions in both cases suggest the involvement of ions and not radicals.

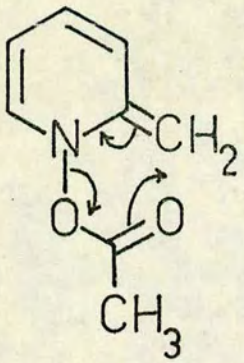
Treatment of isoquinoline 2-oxide (121) with acetic anhydride affords isocarbostyril (122) as the major product,[116] presumably by a similar mechanism to that shown in Scheme 9. The formation of 4-hydroxyisoquinoline (123) as a by-product of this reaction may be explained by the mechanism shown in Scheme 10. If both of the positions α- to the N-oxide group are blocked, substitution with acetic anhydride may take place at the γ-position. Thus, acridine



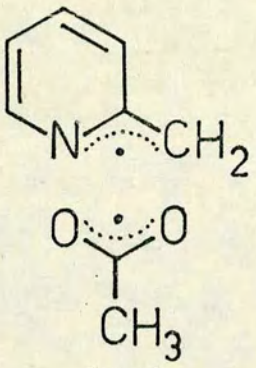
(124) (125)

10-oxide (124) affords acridone (125).[117]

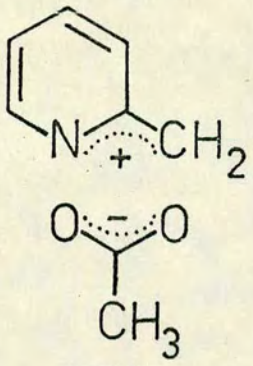
The mechanism of the reaction of 2-picoline 1-oxide (126) with acetic anhydride to give 2-acetoxymethylpyridine (127) has also proved to be somewhat controversial. This reaction with acetic anhydride to give acetoxymethyl derivatives has been shown to be general for α-methylated N-oxides. There is general agreement that the initial step is acylation of the N-oxide group to give the quaternary salt (128) with subsequent proton abstraction to give the anhydro base (129). The intermediacy of the anhydro base is supported by kinetic and spectroscopic measurements.[107,118,119] Kinetic studies suggest that an anhydro base intermediate (cf. 129) is involved in the reaction of 2-methylquinoline 1-oxide with acetic anhydride.[108]



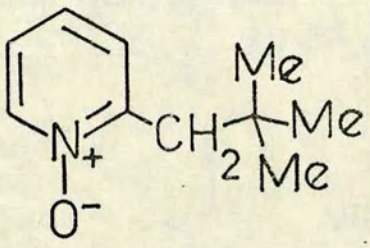
(130)



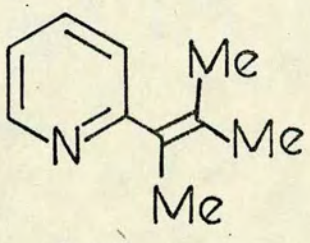
(131)



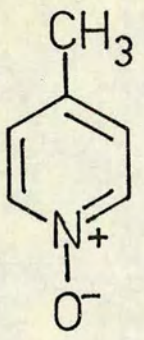
(134)



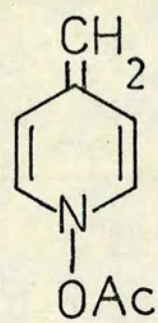
(132)



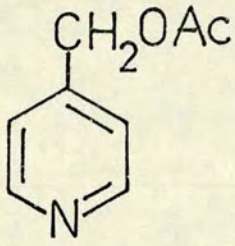
(133)



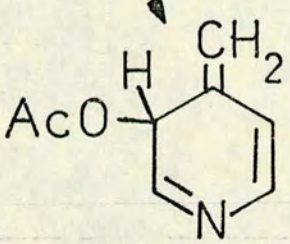
(137)

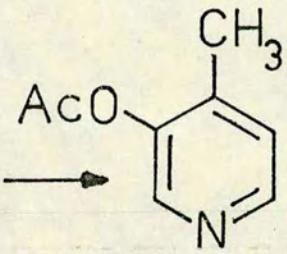


(140)



(138)

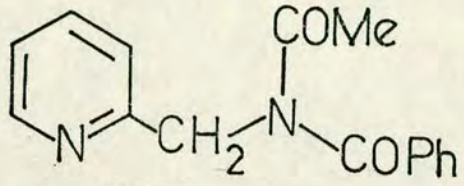




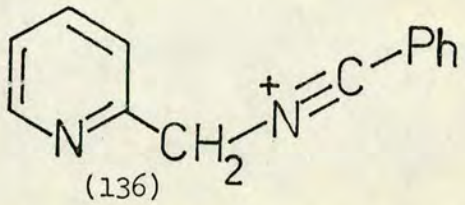
(139)

However, the mechanism of the final rearrangement of the anhydro base (129) to the product (127) has been the subject of considerable controversy. The rearrangement has been shown to be intramolecular by means of cross-over experiments[120] and by the use of isotopic labelling.[121] The latter technique has also been used by Oae[121] to demonstrate that the rearrangement does not occur by an intramolecular pericylcic process (130) as had been proposed earlier.[122] Using acetic anhydride labelled with ^{18}O, Oae found that the two oxygen atoms of the acetoxy group became equivalent during the formation of the product. This result is explained by invoking a radical pair mechanism (131) in which rearrangement occurs within the confines of a solvent cage. Gaseous products derived from free radicals have been isolated from the reaction mixture.[123] However, the reaction of 2-methylpyridine 1-oxide (126) with phenylacetic anhydride gives a good yield of the rearranged ester.[124] If a radical pair mechanism were operating in this reaction the very unstable phenylacetoxy radical would be involved as intermediate and the yield of the rearranged ester should consequently have been low. Further evidence against the radical-pair mechanism was provided by the absence of C.I.D.N.P. emissions in the ^{1}H n.m.r. spectrum of the reacting mixture of (126) and acetic anhydride.[125] Also, the reaction of 2-neopentylpyridine 1-oxide (132) with acetic anhydride gives the olefin (133),[126] suggesting that a carbonium ion-type rearrangement is involved. Summarising the available evidence, the rearrangement of the anhydro base appears to involve mainly an ion-pair process (134) with a minor contribution from a radical-pair process (131).[127] In both cases, the rearrangement takes place within a solvent cage thus explaining the intramolecular nature of the reaction.

The involvement of an ionic mechanism has been further supported by the work of Cohen and Deets[128] who have studied the reaction of 2-picoline 1-oxide (126) with acetic anhydride in the presence of anisole and benzonitrile. In anisole, ortho- and para-picolylanisoles are obtained in addition to the expected product and in benzonitrile, the diacylamine (135) is formed, presumably via the cation (136).



(135)

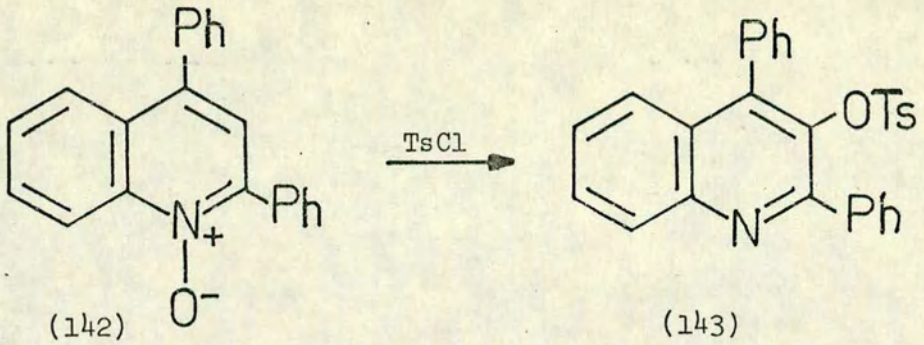


(136)

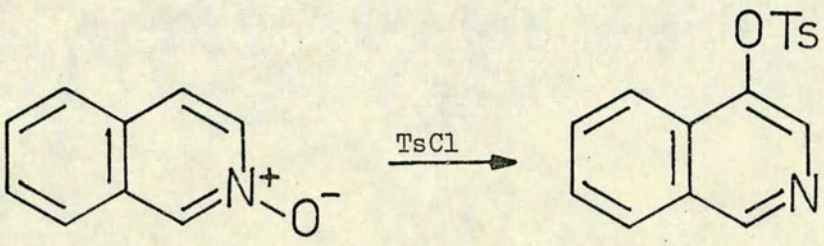
These findings suggest the involvement of cationic intermediates.

The reaction of 4-picoline 1-oxide (137) with acetic anhydride has also been thoroughly investigated but has been found to be more complicated than the analogous reaction of 2-picoline 1-oxide (126). Both 4-acetoxymethylpyridine (138) and 3-acetoxy-4-picoline (139) are formed. Isotopic labelling studies[129] have shown that in the presence of acetic acid or the absence of solvent, the reaction is completely intermolecular. However, in the presence of aromatic solvents, both intermolecular and intramolecular processes appear to be operating with the relative importance of the two processes varying with the nature of the solvent.[129] The work of Cohen and Deets[130] using anisole and benzonitrile as solvents again suggests the involvement of an ionic mechanism. However, recent C.I.D.N.P. studies[131] suggest the possible involvement of free radicals. Thus, the mechanism involved in this transformation is not completely resolved.

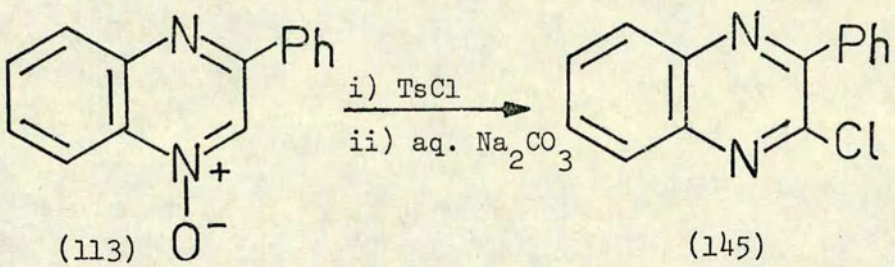
C. Reaction with Sulphonyl Halides.



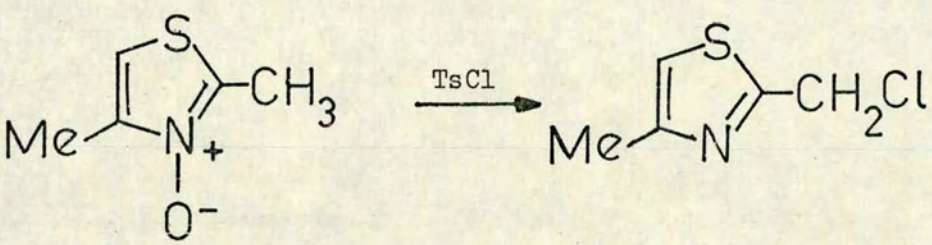
(142) (143)



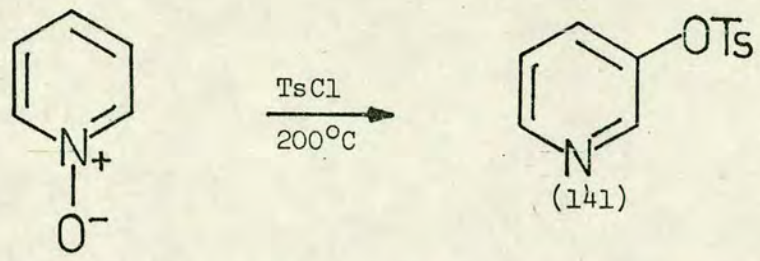
(121) (144)



(113) (145)



(146) (147)

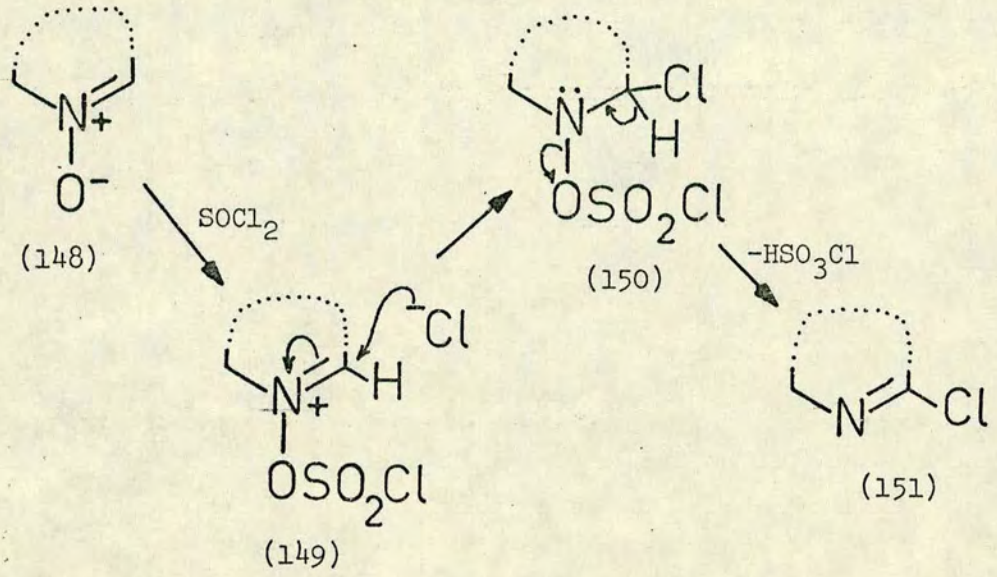


(106) (141)

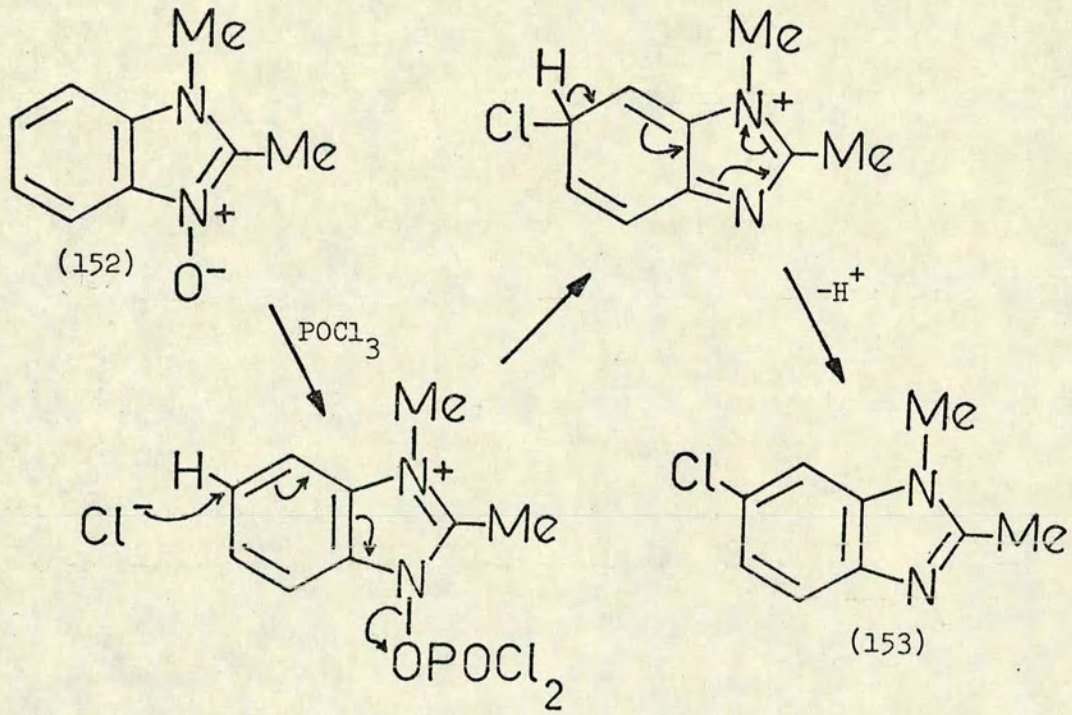
Ts = toluene-4-sulphonyl

Heating pyridine 1-oxide (106) at 200° in the presence of tosyl chloride affords 3-tosyloxypyridine (141).[132] This reaction although it occurs in poor yield is interesting in that the position β to the N-oxide function has been attacked. Similar attack at the β-position or a position conjugated with it occurs in reactions of tosyl chloride with substituted quinoline 1-oxides, isoquinoline 2-oxides and phenazine 5-oxides, in the absence of other nucleophilic reagents. Competing processes take place in the presence of other nucleophiles (see later). Thus, 2,4-diphenylquinoline 1-oxide (142) affords 2,4-diphenyl-3-tosyloxyquinoline (143)[133] and isoquinoline 2-oxide (121) affords 4-tosyloxyisoquinoline (144)[134] in the presence of tosyl chloride. The detailed mechanism of the latter reaction and related processes will be discussed later (Chapter 4).

Some heteroaromatic N-oxides react with tosyl chloride to give chlorinated products. Thus, 3-phenylquinoxaline 1-oxide (113), treated in chloroform, with tosyl chloride followed by aqueous sodium carbonate solution gives, as the major product, 3-chloro-2-phenylquinoxaline (145).[102] If an α-methyl group is present, reaction occurs almost exclusively at the methyl group. Thus, 2,4-dimethylthiazole 3-oxide (146) on treatment with tosyl chloride gives 2-chloromethyl-4-methylthiazole (147).[135]



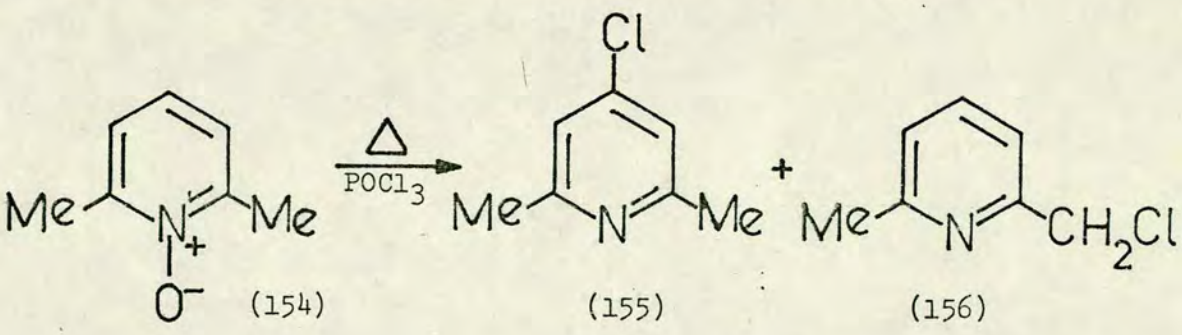
Scheme 11



Scheme 12

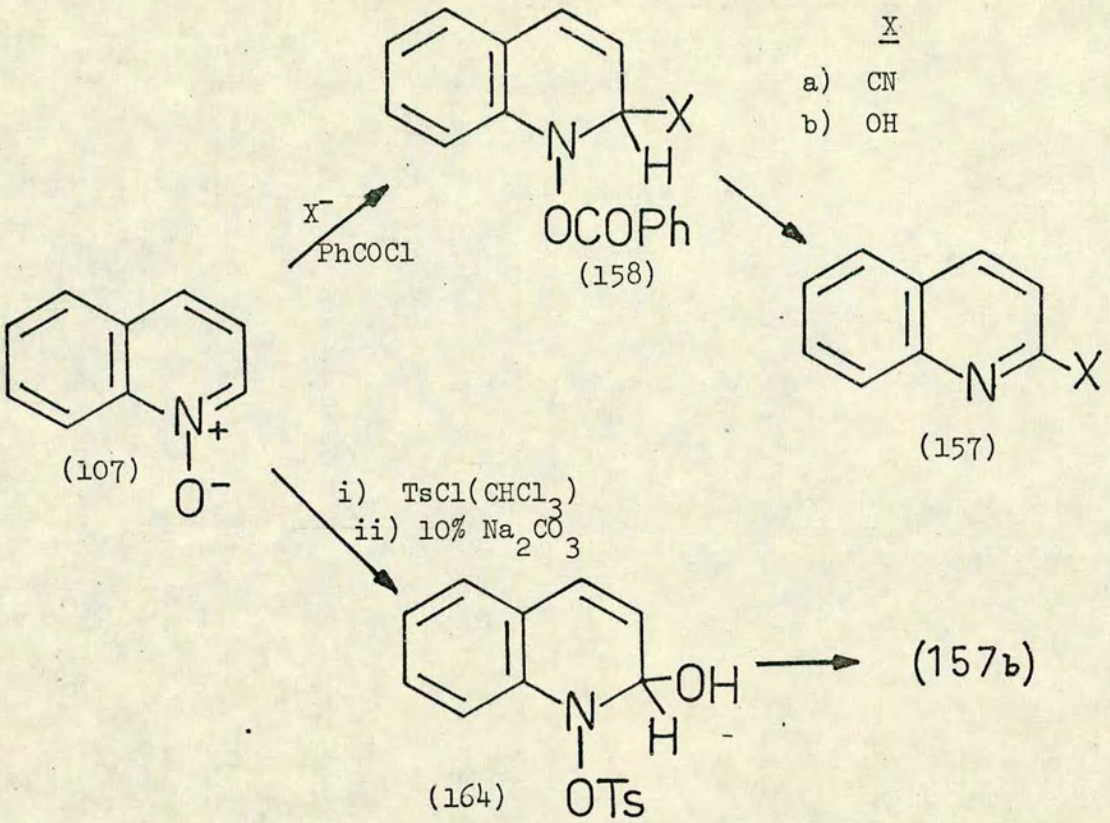
D. Reaction with Inorganic Acid Halides.

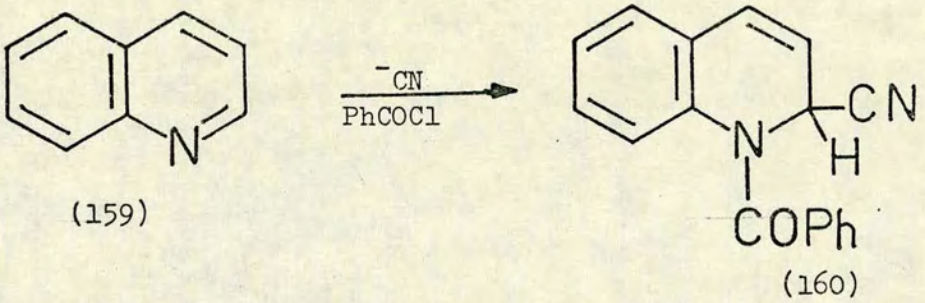
Similar chlorinated products to those mentioned in section (C) before are obtained in the reaction of heteroaromatic N-oxides with phosphoryl chloride or sulphuryl chloride. These halogenation reactions have been shown to occur with heteroaromatic N-oxides in general[136] and are assumed to proceed by the mechanism shown in Scheme 11. Thus, prior co-ordination at the N-oxide oxygen atom gives the intermediate (149) which then undergoes attack by chloride ion at the α-position to afford the adduct (150). Subsequent elimination of the elements of chlorosulphonic acid affords the product (151). In the case of fused heterocycles, substitution may occur in the fused ring if the α-position is blocked. Thus, the reaction of 1,2-dimethylbenzimidazole 3-oxide (152) with phosphoryl chloride affords 6-chloro-1,2-dimethylbenzimidazole (153),[137] presumably by the mechanism shown in Scheme 12. Halogenation of α-methyl substituents may also occur. Heating 2,6-dimethylpyridine 1-oxide (154) with



(154) (155) (156)

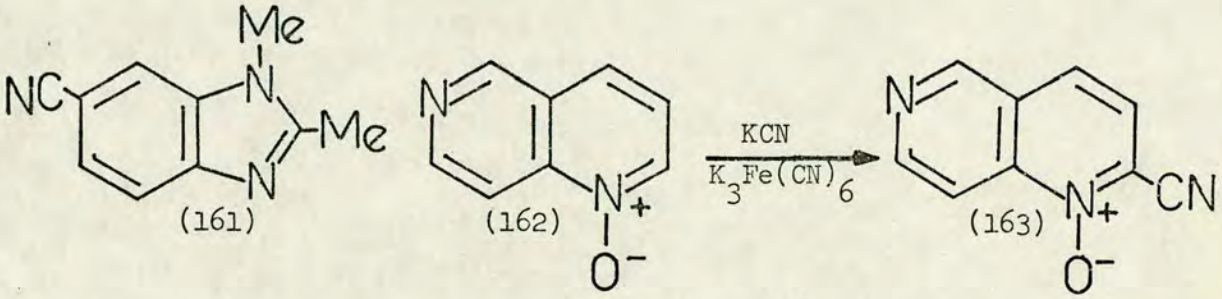
phosphoryl chloride affords 2-chloromethyl-6-methylpyridine (156), as well as 4-chloro-2,6-dimethylpyridine (155) which is the major product.[138]


X
a) CN
b) OH
X⁻
PhCOCl
OCOPh
(158)
(107)
(157)
i) TsCl(CHCl3)
ii) 10% Na2CO3
OH
OTs
(164)
(157b)


⁻CN
PhCOCl
(159)
CN
COPh
(160)

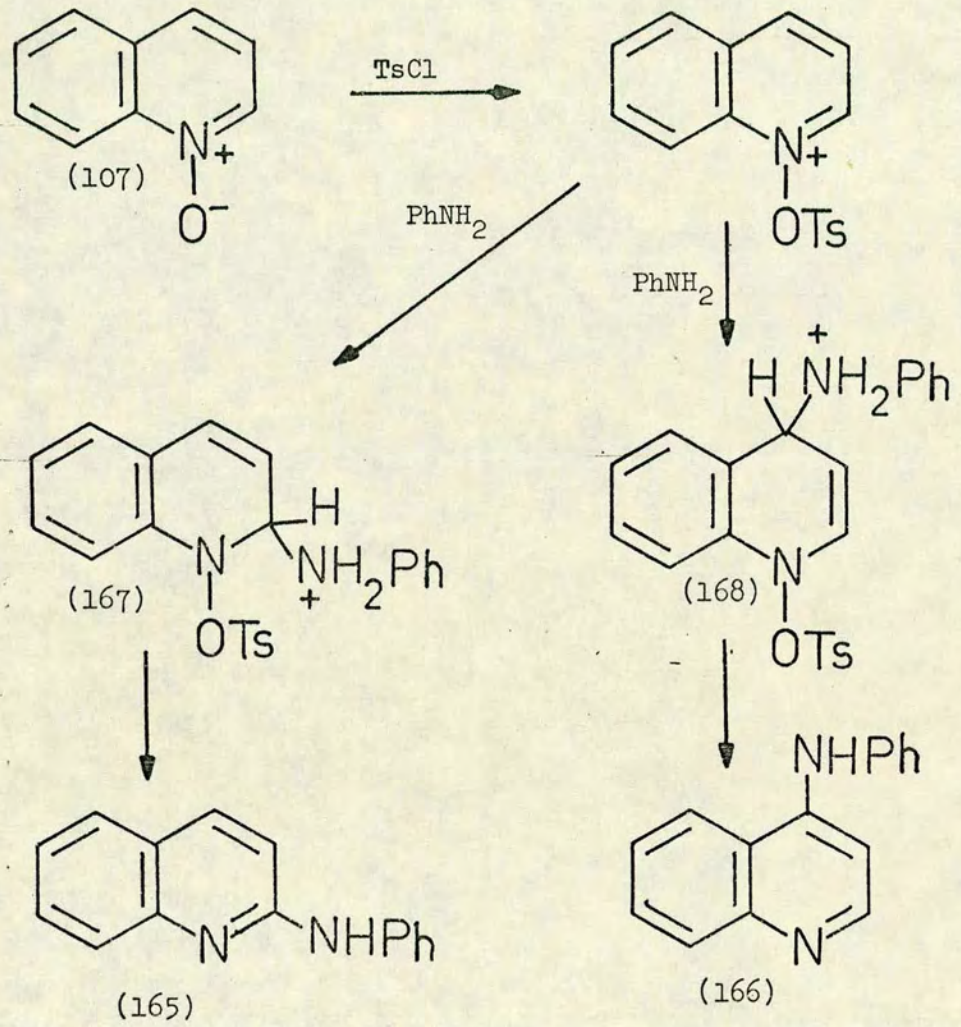
E. Reaction with Anionic Reagents

As has been discussed previously, co-ordination of the N-oxide function increases the susceptibility of the heteroaromatic N-oxide to nucleophilic attack. Thus, the reaction of heteroaromatic N-oxides with cyanide ion in the presence of benzoyl chloride constitutes a general route to cyanoheterocycles. The reaction of quinoline 1-oxide (107) with benzoyl chloride in the presence of cyanide ion affords 2-cyanoquinoline (157a), presumably via the intermediate (158a).[139] This reaction is analogous to the Reissert reaction of quinoline [(159)→(160)][140] but in the reaction with the N-oxide, the intermediate (158a) readily eliminates benzoic acid to give the product (157a). If the α-position is blocked, attack of cyanide ion may occur in a fused ring. Thus, 1,2-dimethylbenzimidazole 3-oxide (152), on treatment with cyanide ion in the presence of benzoyl chloride, affords 6-cyano-1,2-

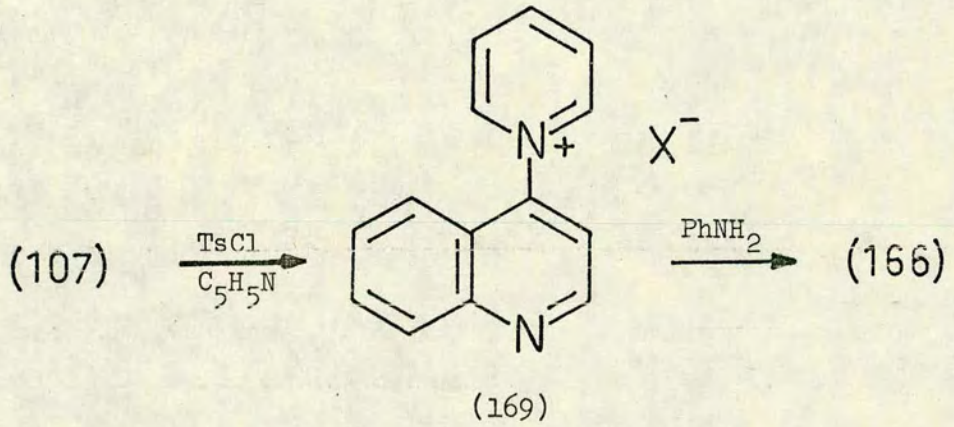


dimethylbenzimidazole (161), via a mechanism analogous to the chlorination of (152) using phosphoryl chloride (Scheme 12).[141] Cyanation with retention of the N-oxide function has also been reported. This is exemplified by the reaction of 1,6-naphthyridine 1-oxide (162) with cyanide ion in the presence of potassium ferricyanide to give 2-cyano-1,6-naphthyridine 1-oxide (163).[142]

The intermediate (158b) involved in the formation of carbostyril (157b) by the substitution of quinoline 1-oxide (107) with hydroxide ion in the presence of benzoyl chloride[143] has been isolated.[144]


TsCl
(107)
PhNH2
PhNH2
OTs
H NH2Ph
(167)
(168)
OTs
OTs
NHPh
NHPh
N
(165)
(166)

Scheme 13


(107)
TsCl
C5H5N
X-
PhNH2
(166)
(169)

This intermediate (158b) readily affords carbostyril (157b) on heating.[144] The intermediate (164) has also been isolated in the analogous reaction of (107) using tosyl chloride as co-ordinating agent and hydroxide ion as nucleophile.[145]

F. Reaction with Amines.

When the reaction of a heteroaromatic N-oxide with tosyl chloride is performed in the presence of an amine, substitution by the amine occurs in the α- or γ-position with concurrent deoxygenation of the N-oxide. Thus, the reaction of quinoline 1-oxide (107) with aniline in the presence of tosyl chloride gives as the major product, 2-anilinoquinoline (165) and as the minor product, 4-anilinoquinoline (166) (Scheme 13).[146] Again, co-ordination of the N-oxide function increases the susceptibility of the ring towards nucleophilic attack by aniline in either the α- or γ-position. Proton abstraction and elimination of toluene-p-sulphonic acid from the resulting intermediates [(167) and (168)] affords the products.

The reaction of quinoline 1-oxide (107) with tosyl chloride in pyridine as solvent affords the 1-(quinolin-4-yl)pyridinium salt (169) which is readily converted into the corresponding aniline derivative (166) by heating with aniline.[147]

The subject matter of the following thesis is concerned with the synthesis of N-oxygenated benzaza-heterocycles and related compounds from ortho-nitrobenzene derivatives and with the scope and mechanisms of the nucleophilic substitution reactions of such compounds in the presence of acylating agents. 1-Phenylcinnolin-4(1H)-ones have been obtained by intramolecular nucleophilic displacement

of the nitro group in substituted ortho-nitrophenacylidene phenylhydrazones. The reactivities of N-oxygenated quinolines, N-oxygenated quinazolines and N-oxygenated quinoxalines towards nucleophilic substitution in the presence of acylating agents have also been studied, with particular emphasis being placed on the mechanisms involved.

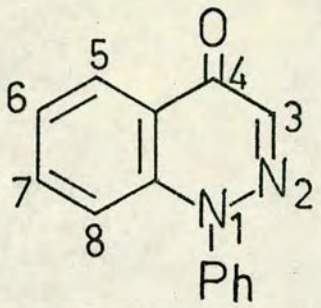
CHAPTER TWO

DISCUSSION

Studies on the Synthesis of Heterocycles from Ortho-Nitrobenzene Derivatives

STUDIES ON THE SYNTHESIS OF HETEROCYCLES FROM ORTHO-NITROBENZENE DERIVATIVES

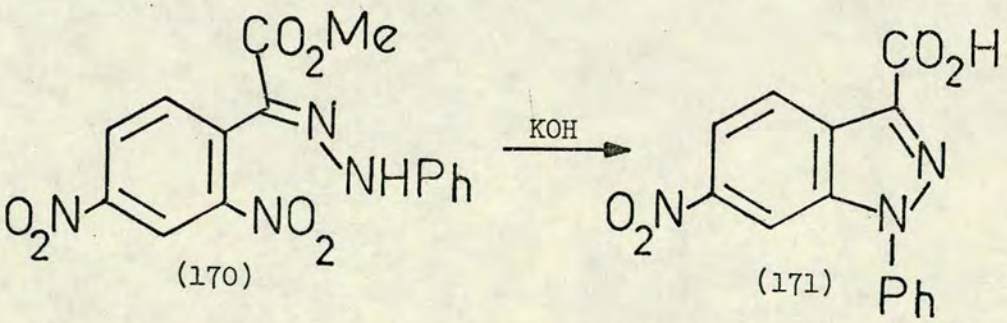
1. Cyclisation by Nucleophilic Displacement of the Nitro Group.



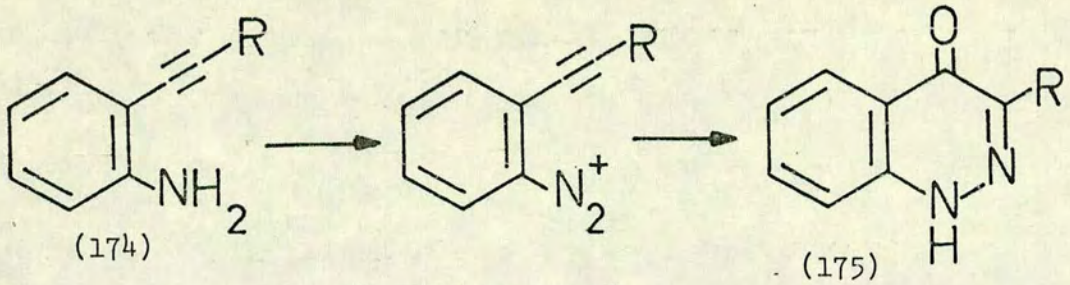
A. 1-Phenylcinnolin-4(1H)-ones

The ease of displacement of suitably activated aromatic nitro groups has been known for a long time, both in an intramolecular and an intermolecular sense. The latter mode of displacement has been of considerable use in the synthesis of interesting and otherwise unobtainable heterocycles.

One of the earliest examples of this type of cyclisation is exemplified by the formation of the 1-phenylindazole (171) by the

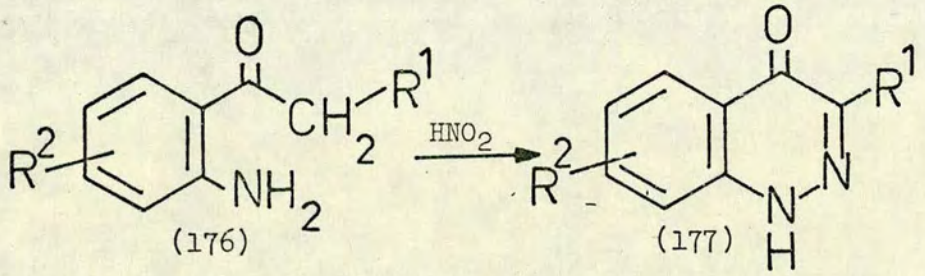


base-catalysed cyclisation of the phenylhydrazone (170).[148] Such cyclisations have since been shown to be general for the arylhydrazones of 2-nitrobenzaldehyde, 2-nitrophenylglyoxalates and 2-methyl-1-(2'-nitrophenyl)glyoxals. The required arylhydrazones are readily available by the coupling of an aryldiazonium salt with the corresponding active methylene compounds:[148]

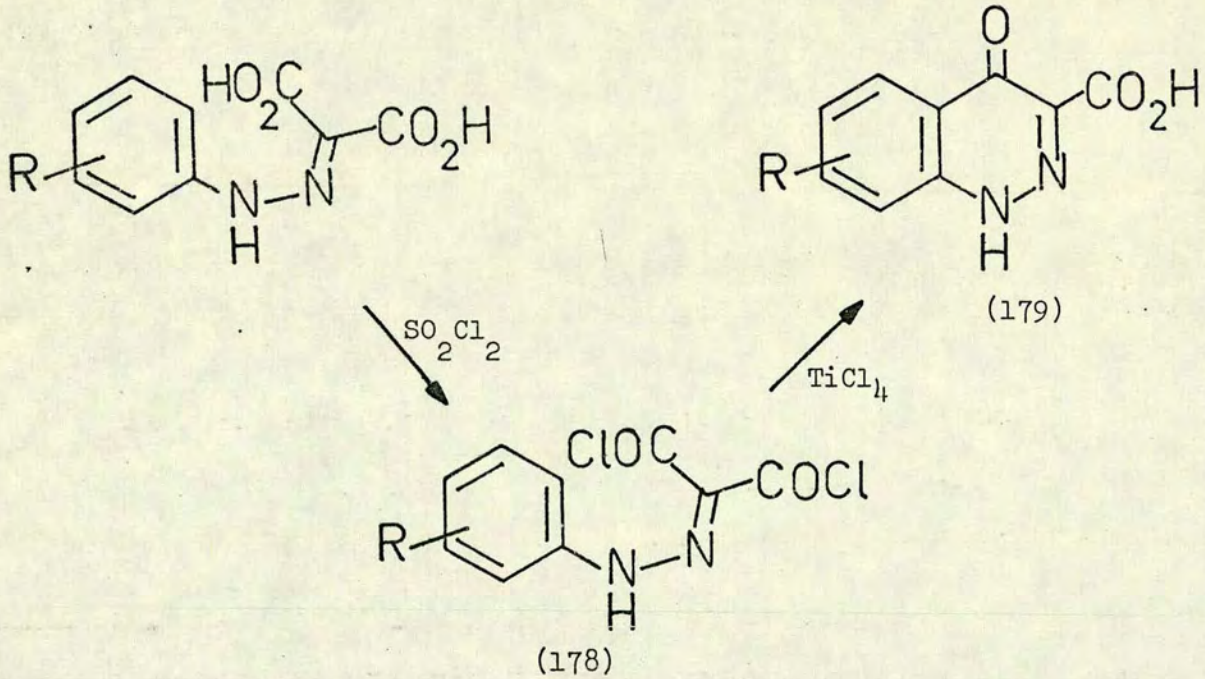


(174) (175)

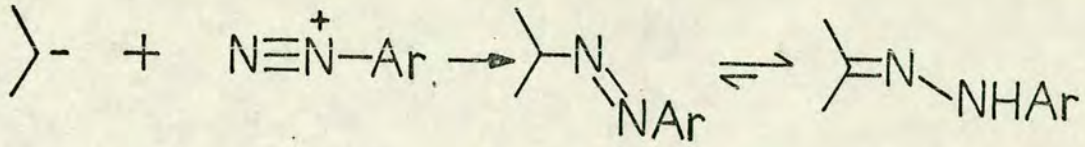
(R = H, Ar, CO_2H)



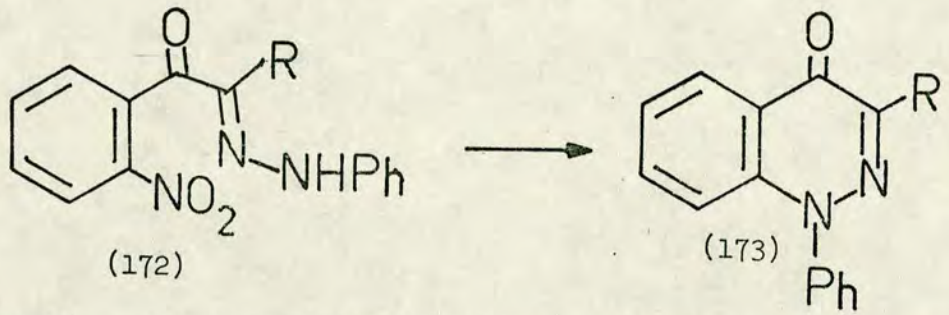
(176) (177)



(178) (179)



A logical extension of this type of cyclisation would involve the formation of a six-membered ring by cyclisation of the structurally similar hydrazones (172) which would also be readily available by the



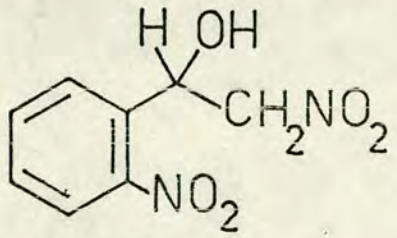
(172) (173)

coupling of benzenediazonium chloride with the appropriate active methylene compounds. The resulting products would be 1-phenylcinnolin-4(1H)-ones (173). By varying the group R in (172), cinnolin-4(1H)-ones containing a variety of functional groups in the 3-position could be obtained by this method. The introduction of a functional group into the 3-position of the cinnoline ring is difficult to achieve using standard cinnoline syntheses, particularly in the case of cinnolin-4(1H)-ones.

Cinnolin-4(1H)-ones may be prepared by the reaction [(174)→(175)] discovered by von Richter[149] and later modified and extended by Schofield and Simpson,[150] which involves diazotisation of 2-aminophenylacetylene derivatives (174). However, this synthesis is only of limited scope because of the relative inaccessibility of the acetylene derivatives. A more versatile synthesis is that of Borsche.[151] This method, which involves the diazotisation of substituted 2-aminoacetophenones (176) has been used in the preparation of a large number of substituted cinnolin-4(1H)-ones (177) containing halogen, alkyl or aryl substituents in the

3-position. Cinnolin-4(1H)-one-3-carboxylic acids (179) may be conveniently synthesised by the intramolecular Friedel-Crafts reaction of readily available mesoxalyl chloride arylhydrazones (178).[152,153]

In view of the relative scarcity of methods for the synthesis of cinnolin-4(1H)-one derivatives it was of interest to investigate the synthesis and cyclisation of 2-nitrophenacylidene phenylhydrazones (181). The latter compounds (181 a-g) were readily prepared by coupling suitable 2-nitrobenzoyl derivatives with benzenediazonium chloride. The requisite 2-nitrobenzoyl derivatives (180 a-d) and (180 g-j) are known compounds and were prepared by the methods described in the literature. The ester (180 c) was obtained from ethyl 2-nitrobenzoylacetoacetate as an oily solid, m.p. < 30°, in only 31% yield as opposed to the high yield reported in the literature.[154] Ethyl 2-nitrobenzoylacetoacetate in turn was obtained in higher yield by the method of Bülow and Hailer[155] (namely by the sodium ethoxide-catalysed condensation of 2-nitrobenzoyl chloride with ethyl acetoacetate using ether as a co-solvent) as opposed to the procedure described by Needham and Perkin.[156] 2,2'-Dinitroacetophenone (180 g)[157] was synthesised by the oxidation of 1-(2'-nitrophenyl)-2-nitroethanol (185)[158] which was in turn prepared by the aldol condensation of nitromethane with 2-nitrobenzaldehyde. The ^{1}H n.m.r. spectrum of the aldol (185) was complicated but can be explained in terms of the non-equivalence of the methylene protons due to the presence of an adjacent asymmetric centre (cf. 185a). Each of the methylene protons (H_B and H_C) gives rise



(185)

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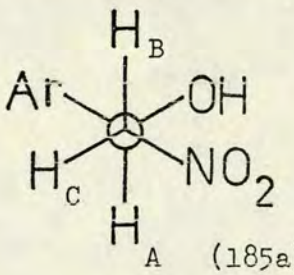


(185a)

to double doublets centred at τ 5.47 and 5.15 respectively with a common geminal coupling constant, J_{BC} 14 Hz. The benzylic proton (H_A) appears

as a double doublet, centred at τ 3.99, due to coupling with each of the methylene protons (H_B and H_C) with coupling constants, J_{AB} 9 Hz and J_{AC} 3 Hz respectively. The absolute positions of H_B and H_C were assigned on the basis of the Karplus equation[159]:-

$$J_{vic.} = A \cos^2 \theta - c$$

where θ is the dihedral angle between the vicinal C-H bonds and A and C are constants. On the basis of this equation the vicinal coupling constant is greatest when the dihedral angle is 0° or 180°. Thus, the larger coupling constant must be due to coupling between the protons, H_A and H_B.

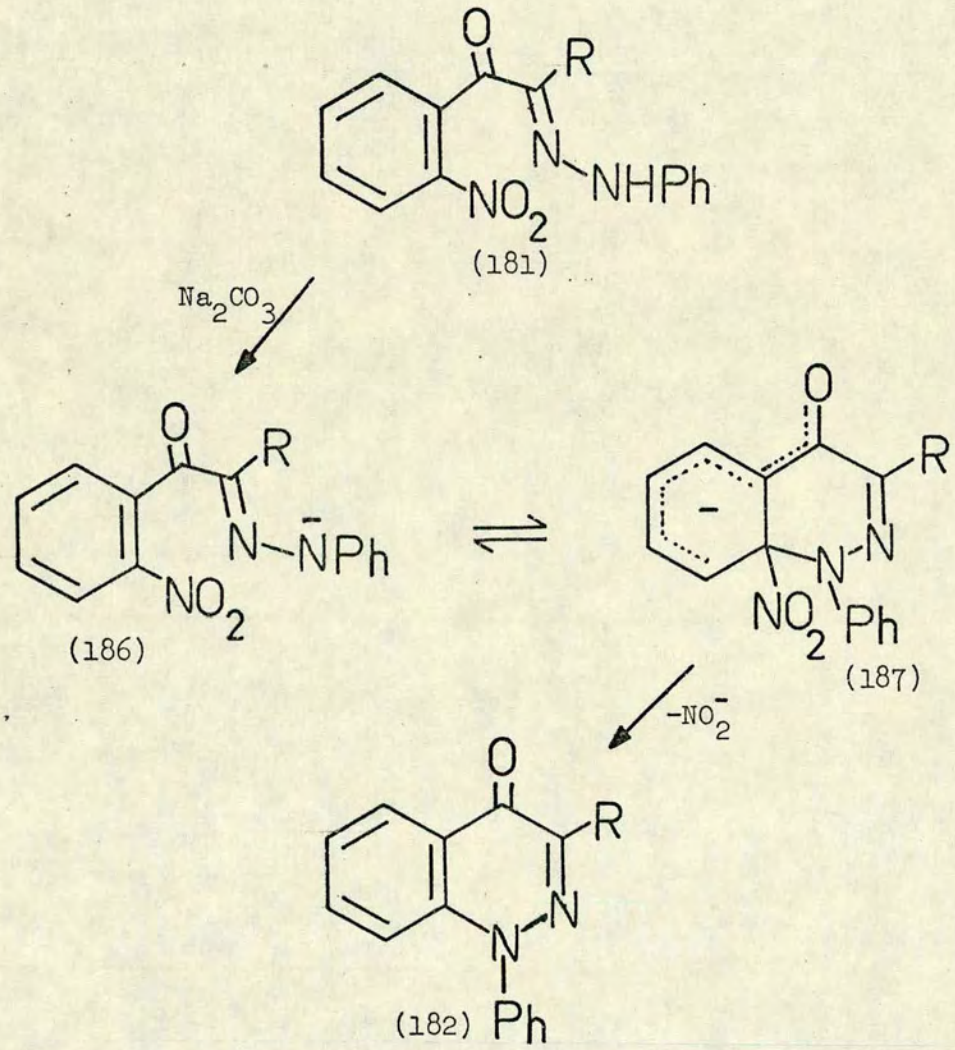
2'-Nitrobenzoylacetamide (180e) was obtained in good yield by mild hydrolysis of the nitrile (180d)[160] using polyphosphoric acid. 2-Benzenesulphonyl-2'-nitroacetophenone (180f) was prepared by nucleophilic substitution of 2-bromo-2'-nitroacetophenone (180i)[161] with sodium benzenesulphinate. The mass spectrum of the sulphone (180f) did not show the parent ion but the structure of this compound is fully in accord with its combustion analysis and i.r. spectrum as well as its conversion into the hydrazone (181f) by coupling with benzenediazonium chloride. The pyridinium salt (180k) was prepared in good yield by the reaction of the bromo compound (180i)[161] with pyridine in dry ether at room temperature.

The diazo coupling reactions were carried out by adding a cold benzenediazonium chloride solution to a solution of the active methylene compound in aqueous ethanol in the presence of sodium acetate (two equivalents) at $10-15^\circ$. The hydrazones (181 a-g) were obtained in high yield as bright yellow solids, all of which were light sensitive. The amide (181e) and the sulphone (181f) both melted over a wide range even after repeated crystallisations. This is probably due to the fact that, as prepared, the phenylhydrazones (181 e and f) are mixtures

of the syn- and anti- isomers. A similar situation is encountered in the case of the corresponding oximes (see later). Due to its insolubility in ethanol, coupling of the dinitro compound (180g) with benzenediazonium chloride was carried out in aqueous acetone giving the hydrazone (181 g) in good yield.

The coupling reaction of benzenediazonium chloride with the pyridinium salt (180 k) in the presence of excess of sodium acetate gave a solid whose i.r. spectrum indicated that it was a mixture of the betaine (183) and its hydrochloride. Treatment of this mixture with aqueous sodium hydroxide effected its conversion in quantitative yield into the orange betaine (183) which decomposed on attempted recrystallisation. The mass spectrum of the betaine (183) lacked a peak due to the parent ion. The peak of greatest mass occurred at m/e 300 which could possibly be assigned to the cinnolin-4(1H)-one (182 l) formed presumably by electron-impact-induced loss of the 2-nitro group. The betaine readily formed a yellow hydrochloride and was readily characterised by means of its picrate derivative. The mass spectra of the hydrochloride and picrate showed a peak at m/e 347 corresponding to the cation of the hydrazone (181 k).

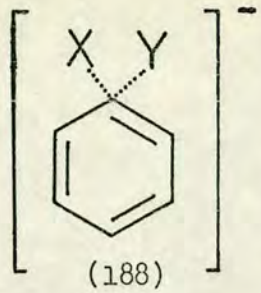
Attempts to synthesise the hydrazones (181 h-j) proved unsuccessful. The reaction of benzenediazonium chloride with the bromo compound (180 i) in the presence of sodium acetate gave an unresolvable three component mixture consisting mainly of starting material. When the reaction was repeated in the presence of sodium ethoxide, unresolvable multi-component mixtures were obtained. The reaction of benzenediazonium chloride with 2'-nitroacetophenone (180 h)[162] in the presence of sodium ethoxide gave only multi-component mixtures. The reaction of benzenediazonium chloride with the carboxylic acid (180 j)[163] in the presence of sodium acetate gave a small amount of an unidentified acidic solid which gave the empirical formula $C_9H_5NO_4$


O
R
N
NHPh
NO2
(181)
Na2CO3
O
R
N
NPh
NO2
(186)
O
R
N
N
NO2
Ph
(187)
-NO2-
O
R
N
N
Ph
(182)

Scheme 14

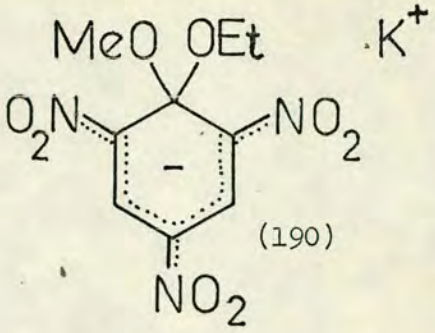
on analysis. The highest peak in the mass spectrum was at m/e 336. It was not possible to assign a structure to fit the spectral and analytical data. The major product of this reaction was a dark red neutral oil which was shown by t.l.c. to contain at least two components. Attempts to resolve the oil into its components using dry-column chromatography were unsuccessful.

The cyclisation of the hydrazones (181 a-g) to the corresponding 1-phenylcinnolin-4(1H)-ones (182 a-h) was conveniently accomplished by heating under reflux in ethanol with 1 N aqueous sodium carbonate solution. The reaction mixtures were initially orange in colour but quickly became red on heating. The colour gradually disappeared after heating for approximately one hour. These colour changes may be explained by the mechanism shown in Scheme 14. The anions (186) formed from the hydrazones (181) are generally orange in colour but on heating, nucleophilic addition to the aromatic ring occurs to give the highly-coloured delocalised anion (187). Elimination of nitrite ion from (187) gives the products (182) which are generally colourless. The overall reaction is in effect a nucleophilic aromatic substitution. There has been considerable controversy concerning the precise mechanism of this type of reaction. Two distinct mechanisms have been suggested, namely, (a) a completely concerted mechanism where the formation of the new bond occurs synchronously with cleavage of the old bond,[164,165] and (b) a two-step mechanism involving addition of the nucleophile to give an intermediate which then eliminates the leaving group to give the product.[78,166] The main difference between the two mechanisms is that the former involves a transition state (188) in which the aromaticity of the ring is retained, whereas the latter involves an intermediate (189) in which the aromaticity of the ring has been destroyed, the driving force for the overall reaction presumably being



(188)

(189)



(190)

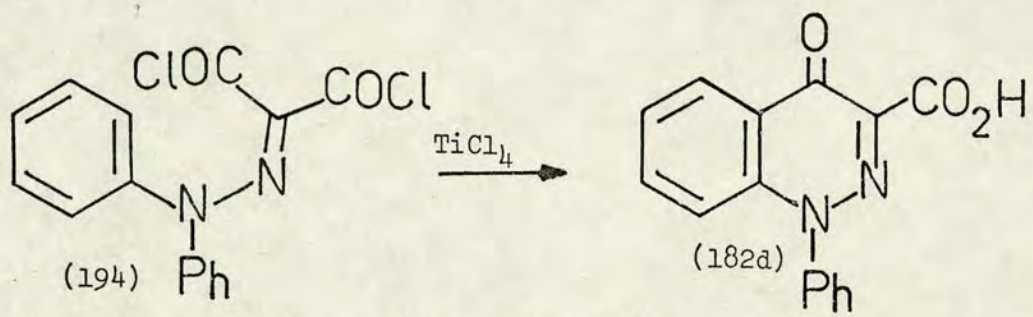
the ultimate rearomatisation of the ring. Theoretical considerations favour the two-step mechanism[78] which is also supported by kinetic studies carried out mainly by Bunnett and his co-workers.[167-169] Further support for the two-step mechanism is provided by the isolation and identification by Meisenheimer[170] of the salt (190) isolated in the reactions of potassium ethoxide with 2,4,6-trinitroanisole or of potassium methoxide with 2,4,6-trinitrophenetole. The salt (190) is analogous to the intermediate (187). Many more of these highly coloured Meisenheimer complexes have since been isolated and characterised.[171] In the light of this evidence, it seems likely that the cyclisation reaction [(181)→(182)] involves an intramolecular nucleophilic substitution by a two-step mechanism via a highly coloured Meisenheimer-type intermediate (187).

The cyclisation of the hydrazone (181 a) gave a two component mixture which on separation by column chromatography gave 3-acetyl-1-phenylcinnolin-4(1H)-one (182 a) in high yield. The minor component of the mixture could not be recovered from the column. The attempted cyclisation of (181 a) using aqueous sodium acetate as catalyst gave a quantitative recovery of starting material.

The acetylcinnolinone (182 a) reacted with hydroxylamine to give a single monoxime which is assigned the structure (191) on the basis of its i.r. spectrum. The parent ketone (182 a) shows i.r. carbonyl bands at 1690 and 1635 cm^{-1}, the higher band arising from the acetyl group. The i.r. spectrum of the monoxime however shows only a band at 1630 cm^{-1}, corresponding to the ring carbonyl, thus indicating that

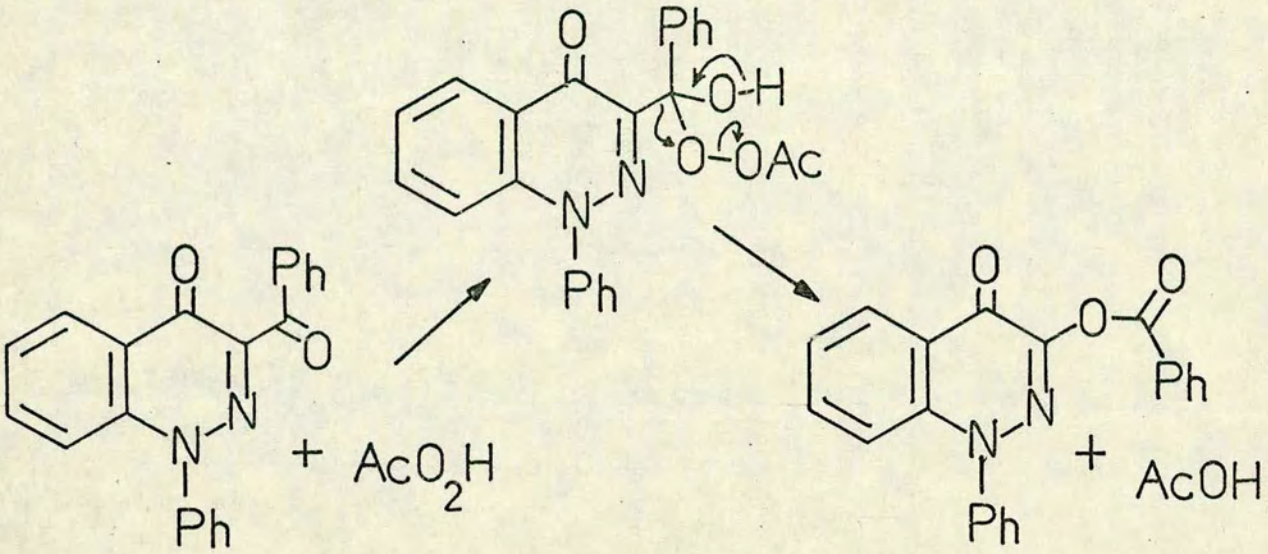
oximation takes place exclusively at the acetyl group. The acetyl compound (182 a) also reacted with hydrazine hydrate to give a monohydrazone which is assigned the structure (192) on the basis of the absence of carbonyl absorption around 1690 cm^{-1} in its i.r. spectrum. Heating the hydrazone (192) under reflux in glacial acetic acid resulted in acid-catalysed cyclisation to the bright red 3-methyl-5-phenylpyrazolo [4,3-c]cinnoline (193).

In the case of the ester (181 c), cyclisation was followed by hydrolysis to give, in addition to the expected 3-ethoxycarbonyl compound (182 c), a moderate yield of 1-phenylcinnolin-4(1H)-one-3-carboxylic acid (182 d). The spectral data and melting point of the latter product show it to be identical to the acid prepared by Barber and Lunt [153] by the intramolecular Friedel-Crafts reaction of mesoxalyl

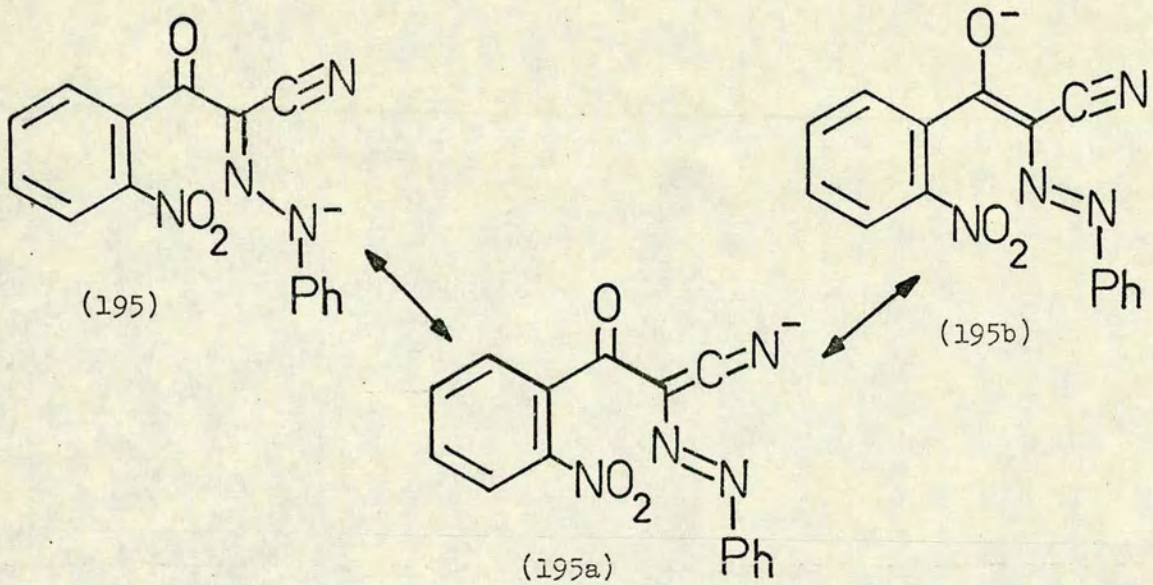


chloride diphenylhydrazone [(194)→(182 d)]. The structure of the 3-ethoxycarbonyl compound (182 c) is thus confirmed since it yields the known acid (182 d) on hydrolysis.

In order to establish the structure of the acetyl compound (182 a), attempts were made to degrade it to a compound of known structure. Attempted hydrolysis using aqueous ethanolic potassium hydroxide gave a greenish-brown solid which was shown by t.l.c. to be an unresolvable multi-component mixture. The acetylcinnolinone (182 a) was found to be stable to acid hydrolysis using aqueous sulphuric acid in glacial acetic acid and to catalytic hydrogenation over 10% palladium charcoal. The structure of (182 a) was however



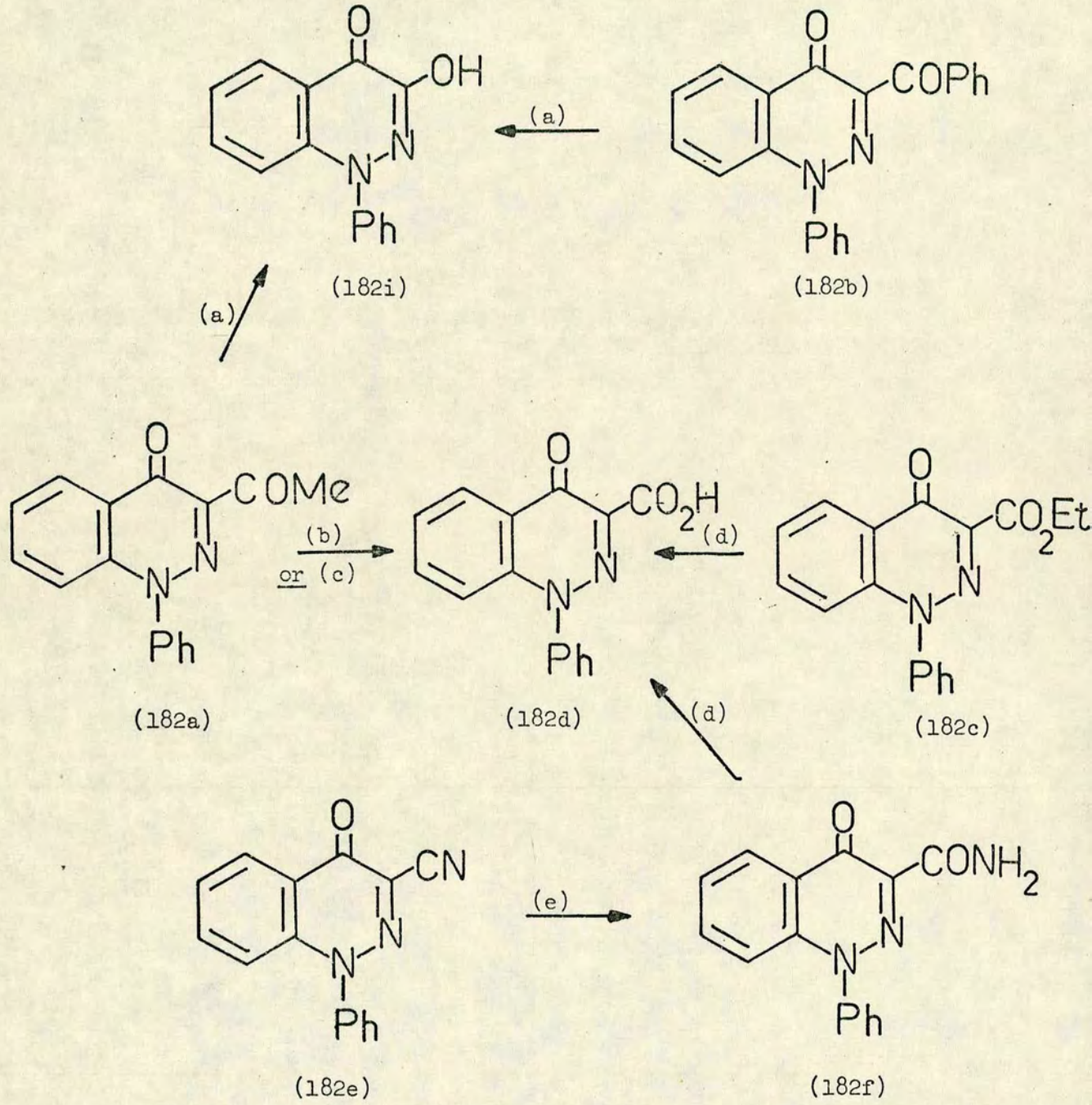
(182b) Scheme 15 (182j)



established by its conversion into the known carboxylic acid (182 d)[153] by oxidation with chromium trioxide in aqueous acetic acid. The cinnolinone (182 a) was also converted into the acid (182 d)[153] by the action of aqueous sodium hypochlorite solution.

The sodium carbonate-catalysed cyclisation of the hydrazone (181 b) gave a good yield of the benzoylcinnolinone (182 b). The structure of (182 b) was established by Baeyer-Villiger oxidation using 30% aqueous hydrogen peroxide in glacial acetic acid. Oxidation of the 3-benzoyl compound (182 b) gave a good yield of 3-hydroxy-1-phenylcinnolin-4(1H)-one (182 i), which was also the product of the similar oxidation of the 3-acetyl compound (182 a), thus confirming the structure of the 3-benzoyl compound (182 b). Also obtained in the oxidation of the benzoylcinnolinone was 3-benzoyloxy-1-phenylcinnolin-4(1H)-one (182 j) whose structure was established by alkaline hydrolysis to the hydroxy compound (182 i) and benzoic acid. The mechanism of Baeyer-Villiger oxidation (Scheme 15) is thought[172] to involve addition of the peracid to the carbonyl group followed by group migration from carbon to oxygen to give the corresponding ester (cf. 182 j). The group which can best accommodate a positive charge migrates preferentially;[172] in the present case, the cinnoline nucleus migrates in preference to either the methyl or phenyl group.

The sodium carbonate-catalysed cyclisation of the nitrile (181 d) gave, in addition to the known[153] carboxylic acid (182 d), a good yield of the amide (182 f). This latter product was shown by spectral data and melting point to be identical to the product obtained in almost quantitative yield from the sodium carbonate-catalysed cyclisation of the amide (181 e). There was, however, no hydrolysis of the cyano group when the cyclisation of (181 d) was carried out using sodium acetate as the base, the nitrile (182 e) being obtained

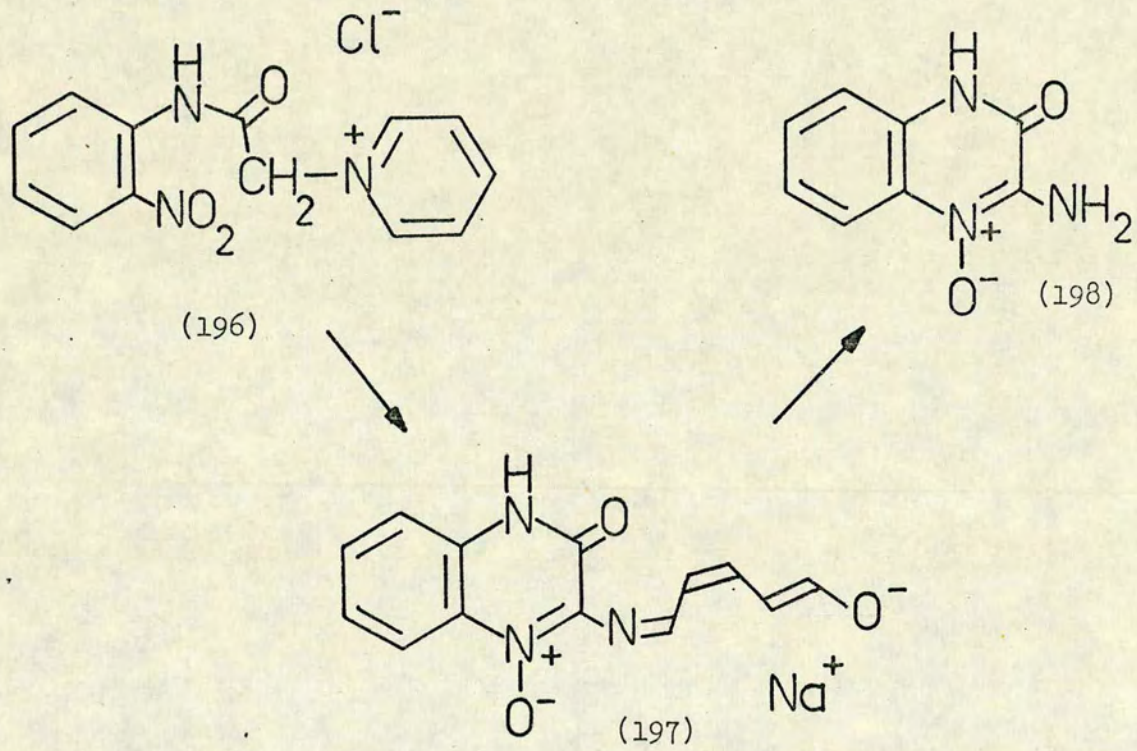


Scheme 16

a) 30% H_2O_2 in AcOH
b) CrO_3 in aq. AcOH
c) NaOCl in aq. Dioxan
d) Na_2CO_3 in aq. EtOH
e) H_3PO_4

in high yield. Both modes of cyclisation of the nitrile (181 d) contrasted with the other hydrazone cyclisations in taking much longer (ca. 40 h) to go to completion. Thus, using sodium carbonate as the base, the amide (181 e) required only 1.75 h to cyclise and significantly, there was no evidence of hydrolysis to the carboxylic acid (182 d) in this reaction. The hydrolysis which accompanies the cyclisation of the nitrile (181 d) in aqueous ethanolic sodium carbonate must therefore occur after the actual cyclisation step. If, in the cyclisation of the nitrile (181 d) the reaction mixture is worked up after only 2 h, an orange sodium salt is obtained which gives starting material (181 d) on acidification. Since the sodium salt is formed quickly, the slow step in the cyclisation must be either the attack of the nucleophile on the ring or the loss of nitrite ion to give the product. If the final step is rate-determining, premature work up of the mixture should give both starting material and product. Also, the reaction mixture should be highly coloured due to the presence of a high proportion of the intermediate (187; R = CN) whereas in fact it is only pale orange in colour. So, it seems likely that the nitrile is exerting a stabilising influence on the initially formed anion (195) thus hindering rate-determining nucleophilic attack on the ring. Resonance forms (195 a) and (195 b) will contribute to the stabilisation of the anion (195) but similar resonance forms are possible for the anions derived from the hydrazones (181 a-c and e-g). Consequently, there appears to be no obvious explanation for the exceptional sluggishness of the cyclisation of the nitrile (181 d). The structure of the nitrile (182 e) was established by mild hydrolysis (using polyphosphoric acid) to the amide (182 f) whose structure was in turn confirmed by its further hydrolysis to the known acid (182 d).[153] The relationships of the cinnolinones (182 a-c, e, f and i) to the known[153] compound (182 d) are shown in Scheme 16.

Cyclisation of the hydrazone (181 g) to the nitrocinnolinone (182 h) was accomplished using either sodium carbonate or sodium acetate as the base. However, both modes of cyclisation resulted in some decomposition due to the instability of the hydrazone (181 g) which partly decomposed even on crystallisation. Consequently, the yield of the nitrocinnolinone (182 h) was low. This compound is assigned the cinnolinone structure (182 h) by analogy with the products of the other cyclisations. This structural assignment is supported by spectral and analytical data. The i.r. spectrum shows bands at 1540 and 1320 cm^{-1} indicating the presence of a nitro group and a band at 1660 cm^{-1} can be assigned to the ring carbonyl group. Typically, the cinnolinones (182 a-f) show carbonyl absorption in their i.r. spectra in the range 1620-1645 cm^{-1}. The slightly higher frequency for the carbonyl group in the nitro compound (182 h) may be due to the strong electron-withdrawing effect of the nitro group. The mass spectrum of (182 h) shows the parent ion peak at m/e 267. These data are consistent with the assigned structure (182 h). The attempted hydrolysis of the nitrocinnolinone (182 h) to the hydroxy compound (182 i) using 20% w/v aqueous sulphuric acid in glacial acetic acid was unsuccessful, giving a high recovery of the starting material. The attempted catalytic reduction of (182 h) to the 3-aminocinnolinone (182 k) was also unsuccessful. Three molar equivalents of hydrogen were absorbed but the solid product, although exhibiting i.r. and mass spectra consistent with the expected amine (182 k), was shown by t.l.c. to be a two component mixture which could not be separated by crystallisation from ethanol. Dry-column chromatography of the reduction product over alumina gave a very small quantity of a pure solid whose i.r. and mass spectra were fully in accord with the expected amine (182 k). However, there was insufficient material for further characterisation. The remainder of the material recovered from the column was shown by t.l.c. to be a three component mixture which suggested that some reaction had


Cl⁻
H
N
O
CH2
N+
NO2
(196)
H
N
O
NH2
N+
O⁻
(198)
H
N
O
N
O⁻
N+
O⁻
Na+
(197)

occurred on the column. This mixture proved to be inseparable by preparative t.l.c. over alumina. The attempted acetylation of the crude reduction product gave a red solid whose i.r. spectrum showed bands at 3300 (NH) and 1700 (CO) cm^{-1}, consistent with it being an N-acetyl derivative. Again, however, t.l.c. showed the acetylation product to be an unresolvable two component mixture.

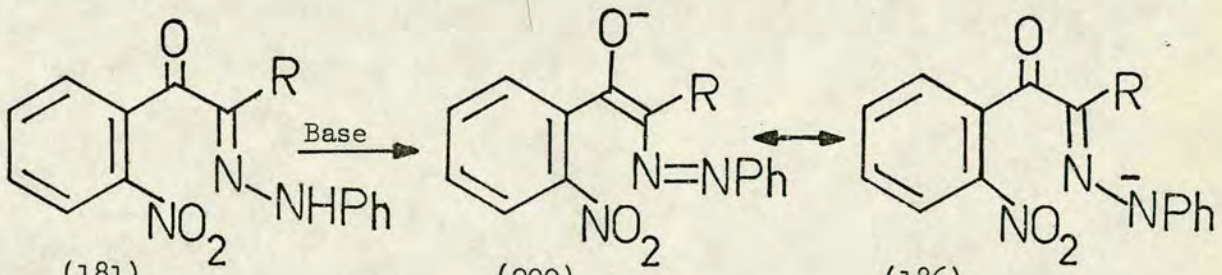
Sodium carbonate-catalysed cyclisation of the hydrazone (181 f) gave the benzenesulphonylcinnolinone (182 g) in good yield. The product is assigned the structure (182 g) by analogy with the other cinnolinone products and also on the basis of spectral and analytical data. The mass spectrum shows the parent ion peak at m/e 362 and the i.r. spectrum contains a band at 1635 cm^{-1}, assigned to the ring carbonyl.

Cyclisation of the betaine (183) using aqueous ethanolic sodium carbonate solution gave a yellow product formulated as 3-(5-oxopent-2-enylidene)amino-1-phenylcinnolin-4(1H)-one (184). In this case, initial cyclisation to give the pyridinium salt (182 l) is presumably followed by ring-opening to give the product (184). The similar ring-opening of a pyridine ring is presumed to be involved in the base-catalysed cyclisation of the pyridinium salt (196) to the 2-amino-quinoxaline 1-oxide (198).[173] The intermediate anil in this reaction, analogous to (184), has been isolated as its sodium salt (197).[174] The structure (184) is assigned on the basis of mass spectral and analytical evidence. The ^1H n.m.r. spectrum of (184) could not be obtained, due to the insolubility of the solid in organic solvents, such as dimethyl sulphoxide or chloroform, and its rapid decomposition in trifluoroacetic acid. Attempts to establish the structure of (184) by hydrolysis or reaction with aniline[175] to give the corresponding aminocinnolinone (182 k) were unsuccessful, resulting in the formation of intractable highly coloured gums from which no identifiable material could be

obtained. The attempted hydrogenolysis of the cinnolinone (184) gave only a multi-component mixture which could not be characterised. An attempt to cyclise the betaine (183) thermally, in the absence of base, also failed.

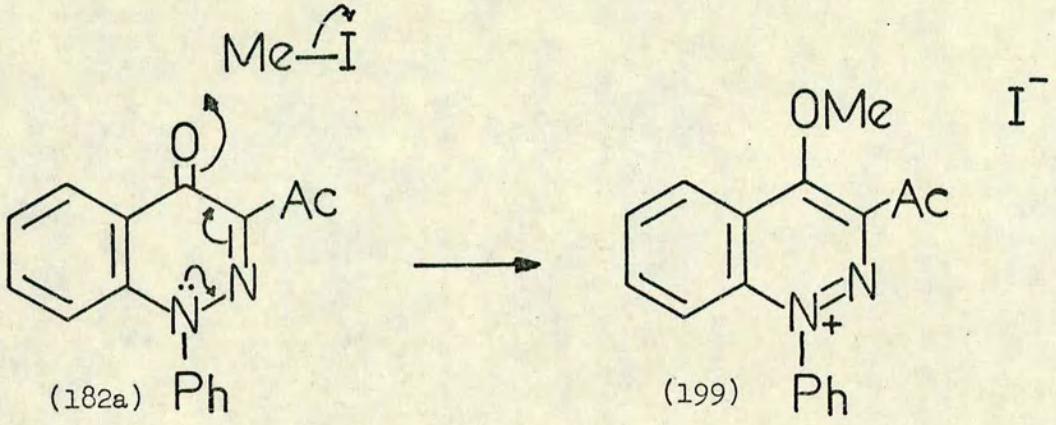
It was of interest to determine whether or not the 1-phenylcinnolin-4(1H)-one ring could be quaternised as shown [(182 a)→(199)]. However, the attempted methylation of the 3-acetyl compound (182 a) using methyl iodide in methanol was unsuccessful giving a quantitative recovery of starting material.

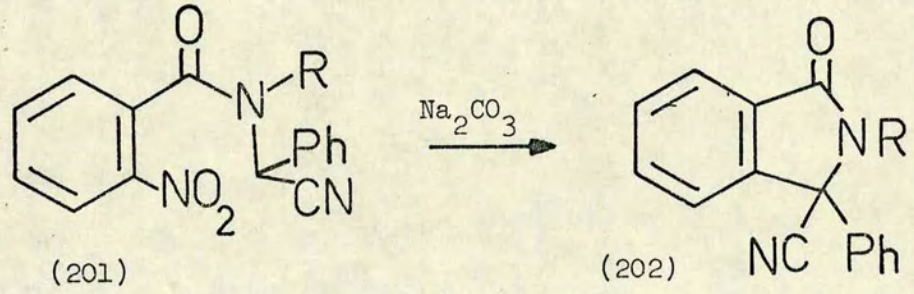
The use of the weak bases, sodium carbonate and sodium acetate, as catalysts in the cyclisations of the hydrazones (181 a-g) demonstrates the ease of displacement of the nitro group in these cyclisation reactions. The analogous cyclisation of the hydrazone (170) to the 1-phenylindazole (171)[148] using strong alkali requires much more vigorous conditions. There are two factors which enhance the ease of cyclisation of the phenacylidene hydrazones. Firstly, the phenacylidene hydrazones (181 a-g) are much more acidic than the simple hydrazones (cf. 170) since the negative charge of the derived anion may be more fully

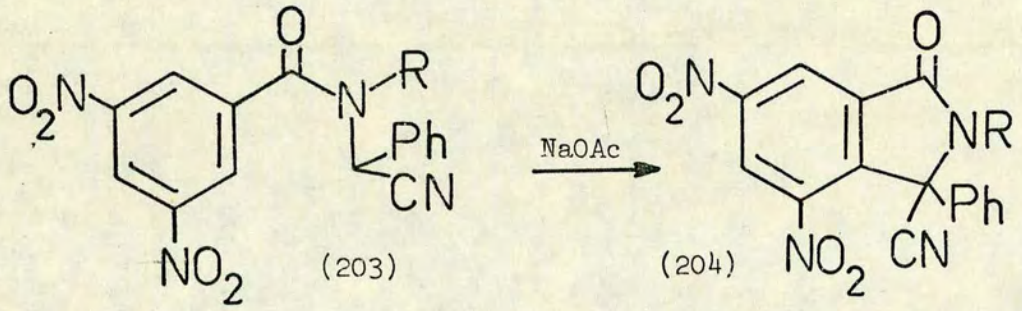


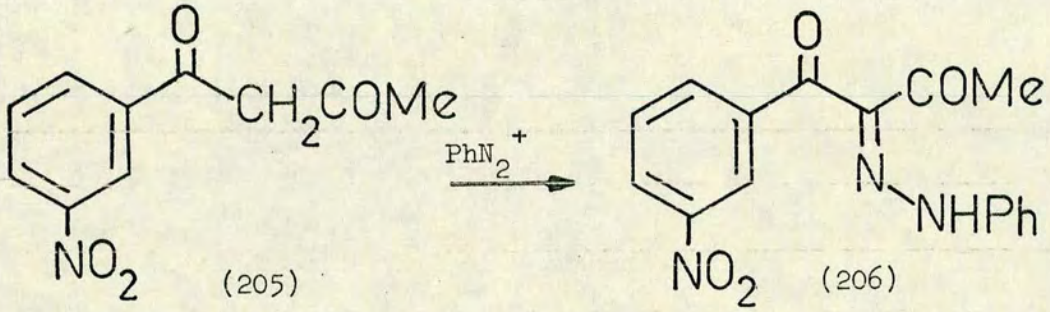
(181) (200) (186)

delocalised in the phenacylidene case due to the contribution of the additional resonance form (200). Secondly, the relatively mild conditions required for cyclisation of the hydrazones (181 a-g) may also be due to the sterically favourable formation of a six-membered cyclic intermediate (187), as opposed to the five-membered cyclic intermediate involved in indazole formation [(170)→(171)].[148]


Me—I
O
Ac
N
N
Ph
(182a)
OMe
I⁻
Ac
N
N+
Ph
(199)


O
N
R
Ph
CN
NO2
(201)
Na2CO3
O
NR
NC
Ph
(202)

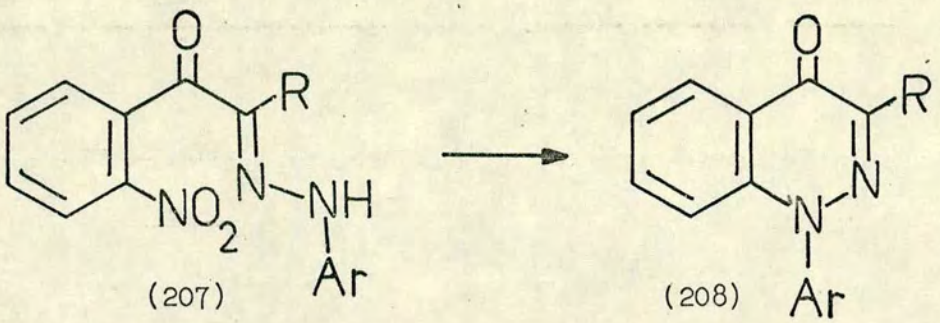

O2N
O
N
R
Ph
CN
NO2
(203)
NaOAc
O2N
O
NR
Ph
NO2
CN
(204)


O
CH2COMe
NO2
(205)
PhN2+
O
COMe
N
NHPh
NO2
(206)

A synthesis of isoindolin-1-ones (202) involving the intramolecular nucleophilic displacement of aromatic nitro groups by carbanion centres in ortho-side chains [(201)→(202)] has been described recently.[176] This type of cyclisation has been extended to include the novel intramolecular nucleophilic displacement of hydride ion as exemplified by the process [(203)→(204)].[177] In the present studies an attempt was made to effect the similar cyclisation of the phenacylidene hydrazone (206). This substrate was readily prepared in high yield by coupling the known[8] compound, 3′-nitrobenzoylacetone (205) with benzenediazonium chloride.

The attempted cyclisation of the hydrazone (206) using aqueous ethanolic sodium carbonate gave a brown solid which was shown by t.l.c. to be a five component mixture. Dry-column chromatography over alumina failed to effect a separation of the components of the mixture and no identifiable material was obtained. It was found in the isoindolin-1-one synthesis [(203)→(204)][177] that substantially increased yields were obtained when the cyclisation was performed in the presence of para-benzoquinone. Consequently, the cyclisation of (206) was attempted in the presence of an equimolar quantity of para-benzoquinone. A black reaction mixture resulted and the material isolated on work up was shown by t.l.c. to be a more complicated mixture than that obtained in the absence of para-benzoquinone. These reactions of the hydrazone (206) were not investigated further.

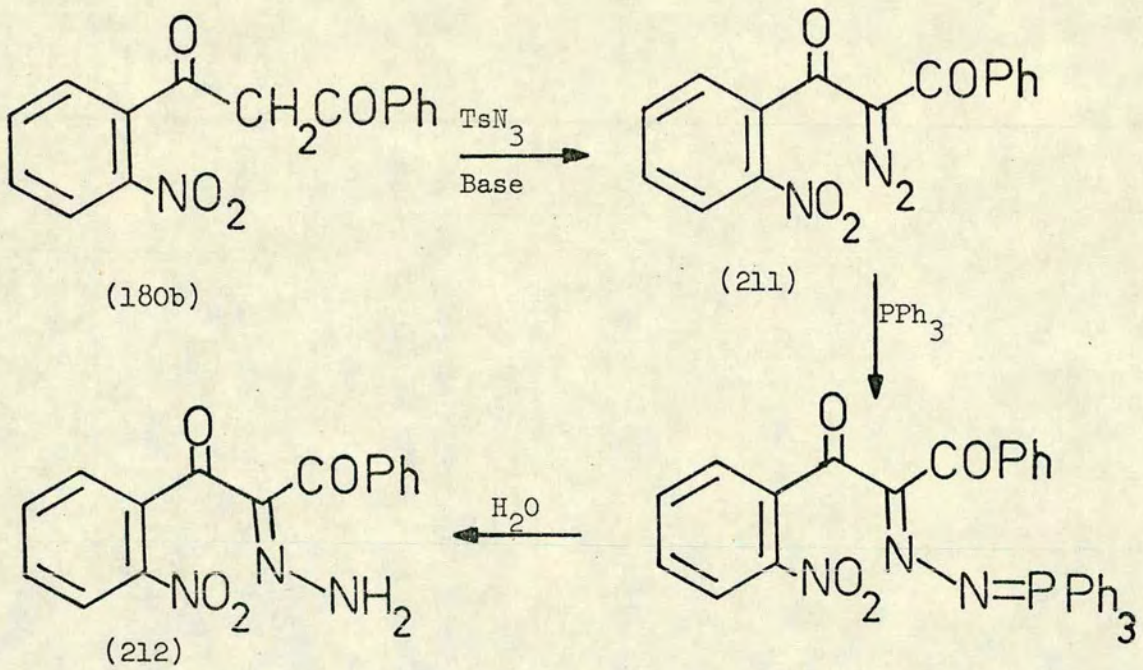
As applied to 2′-nitrophenacylidene phenylhydrazones, the cinnolinone cyclisation is limited to the synthesis of 1-phenyl derivatives. The scope and utility of this cinnolinone synthesis would be greatly enhanced if the cyclisation of 2-nitrophenacylidene hydrazones (or N-substituted derivatives containing readily removable substituents) could be achieved since the products would then be the parent cinnolinones. With this objective in mind, an attempt was made to synthesise benzothiazolyl-hydrazones (207) which should undergo cyclisation to cinnolinones of the type (208) containing an N-benzothiazolyl substituent, the ready



(207) (208)

(Ar = 2-Benzthiazolyl)

(209) (210)



(180b) (211) (212)

Scheme 17

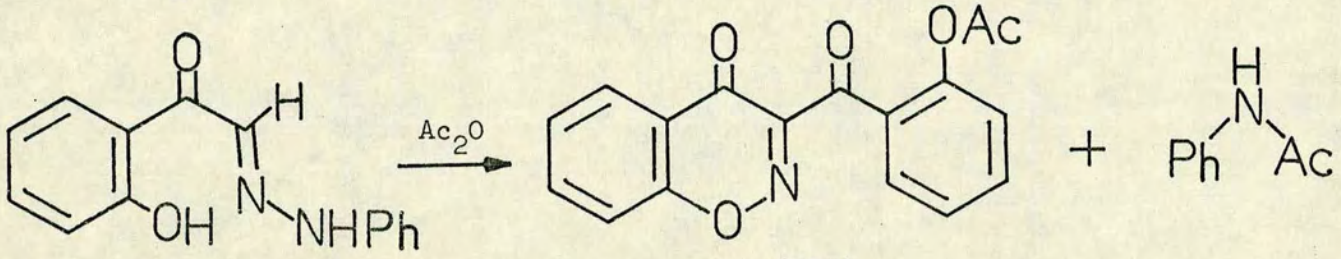
removal of which would afford the otherwise inaccessible cinnolinones (209). However, this extension to the cinnolinone synthesis was thwarted by the failure of attempts to diazotise 2-aminobenzthiazole (210) under conditions suitable for coupling with the requisite active methylene compounds.

In another attempt to synthesise the parent 3-substituted cinnolinones (209), the known hydrazone (212) was prepared using the method of Regitz[178] as shown in Scheme 17. The attempted cyclisation of the hydrazone (212) in aqueous ethanolic sodium carbonate or sodium acetate resulted in extensive decomposition of the starting material with formation of unresolvable multi-component mixtures. An attempt to form the tosylhydrazone (212: toluene-p-sulphonyl for H) by the reaction of the hydrazone (212) with tosyl chloride in pyridine was unsuccessful giving an 86% recovery of the starting material. In another approach, the diazo compound (213) was prepared from the diketone (180a) as described by Regitz.[178] Treatment of (213 b) in hot ethanol with aqueous potassium

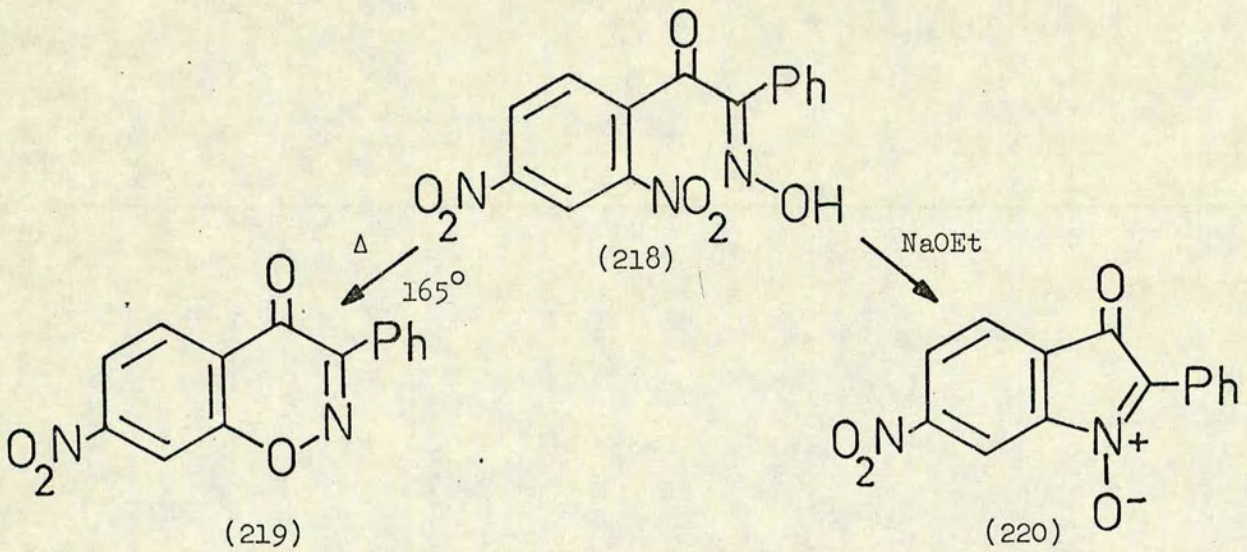
(213) (214)

a) R = H
b) R = NO_2

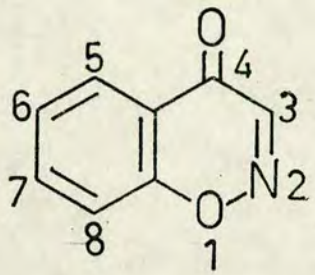
cyanide gave the cyanohydrazone (214 b) which could not be characterised due to its decomposition on attempted recrystallisation. The i.r. spectrum of the crude product showed the presence of a cyano group (2250 cm^{-1}) as well as NH absorption (3300 cm^{-1}) and the absence of an acetyl group (no band at ca. 1690 cm^{-1}). The ^1H n.m.r. spectrum in hexadeutero-dimethyl sulphoxide also lacked acetyl absorption and showed a sharp singlet at τ 2.22 due to the phenacylidene C-H proton.


O
H
OH
N
NHPh
Ac2O
O
O
OAc
N
O
+
H
N
Ph
Ac

(216) (217)

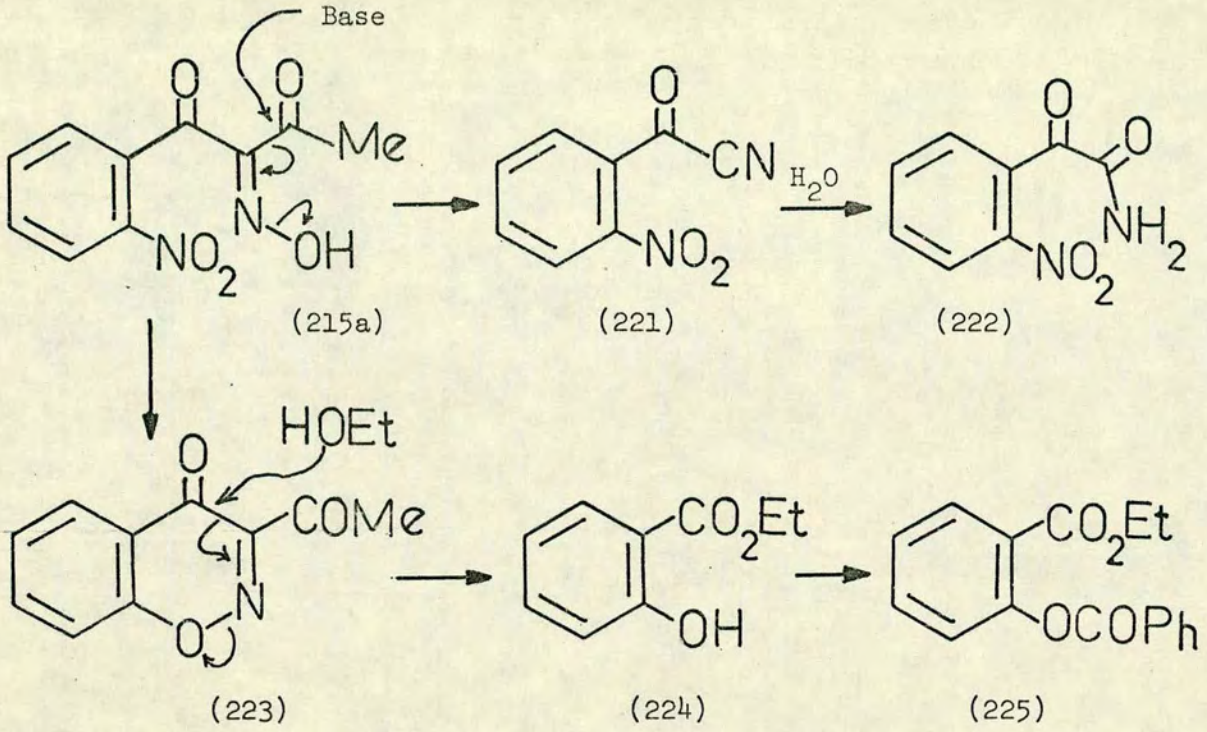

O
Ph
O2N
NO2
N
OH
(218)
Δ
165°
NaOEt
O
Ph
O2N
N
O
(219)
O
Ph
O2N
N+
O-
(220)

The structure (214 b) is therefore assigned to the crude product on the basis of its spectral properties and by analogy with the similar formation of the cyanohydrazone (214 a) from the diazobenzoylacetone (213 a).[179] The attempted cyclisation of the crude cyanohydrazone (214 b) in aqueous ethanolic sodium carbonate solution gave a pale brown solid those t.l.c. showed it to be a mixture of the starting material (214 b) and one other component. This solid decomposed before it could be investigated further.

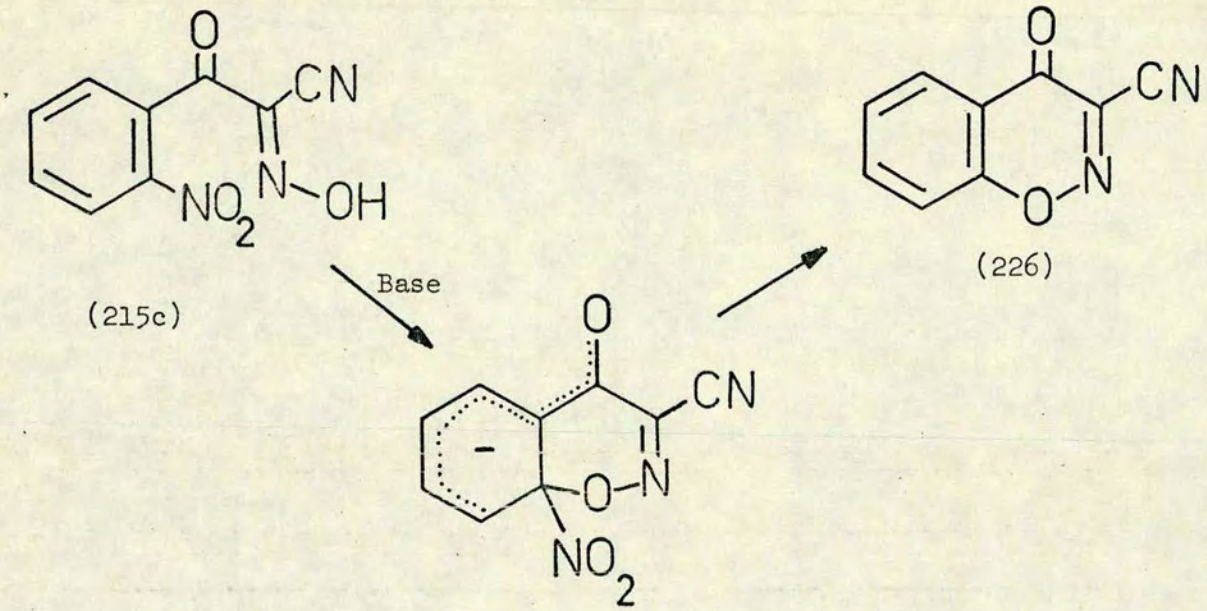


B. Benz-1,2-oxazin-4-ones

The successful cyclisation of the hydrazones (181 a-g) prompted an investigation into the base-catalysed reactions of the analogous oximes (215 a-c). If these were to cyclise in a similar fashion to the hydrazones (181 a-g), the products formed would be benz-1,2-oxazin-4-ones. In contrast to the isomeric benz-1,3-oxazinone, benz-1,4-oxazinone, and benz-2,3-oxazinone ring systems, of which there are many examples, reports of the benz-1,2-oxazin-4-one ring system are comparatively rare. The benz-1,2-oxazinone (217) is reported to be formed together with acetanilide when the 2-hydroxyphenacylidene phenylhydrazone (216) is heated under reflux in acetic anhydride.[180] An earlier report describes the formation of the benz-1,2-oxazinone (219) by the action of heat on an alcoholic solution of the 2,4-dinitrobenzilmonoxime (218).[181] The base-catalysed reaction of the oxime (218) however gave the isomeric isatogen (220).[181] The reactions [(218)→(219)]

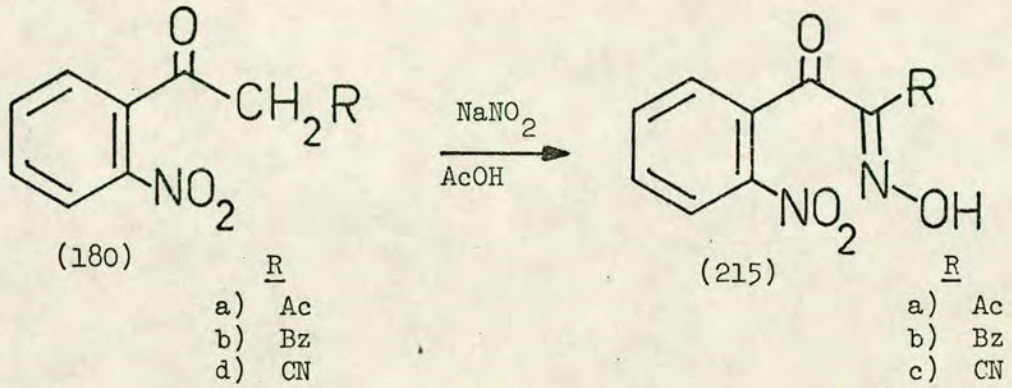

Base
Me
N
OH
NO2
(215a)
CN
NO2
(221)
H2O
O
NH2
NO2
(222)
HOEt
COMe
N
O
(223)
CO2Et
OH
(224)
CO2Et
OCOPh
(225)

Scheme 18


CN
N
OH
NO2
(215c)
Base
CN
N
O
NO2
CN
N
O
(226)

and [(218)→(220)] involve intramolecular nucleophilic displacement of a nitro group and are thus very similar to the hydrazone cyclisations [(181)→(182)] and hence to the base-catalysed reactions of the oximes (215 a-c) which will now be discussed.

The oximes (215 a-c) were prepared in good yield by nitrosation



(180)

R
a) Ac
b) Bz
d) CN

(215)

R
a) Ac
b) Bz
c) CN

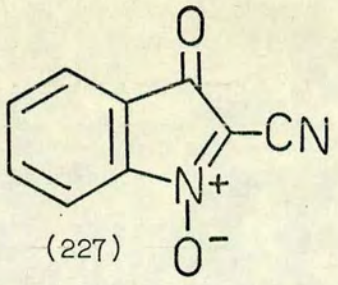
of the active methylene compounds (180 a,b and d). All three oximes were obtained as mixtures of the syn- and anti- forms as indicated by their indefinite melting points.

The attempted cyclisation of 1-(2-nitrophenyl)-2-oximinobutane-1,3-dione (215 a) using aqueous ethanolic sodium carbonate or sodium acetate gave low yields of the known[182] compound 2-nitrophenylglyoxylamide (222) and ethyl salicylate (224) together with 2-nitrobenzoic acid and ethyl 2-nitrobenzoate. The amide (222) was identified by its i.r. spectrum, elemental analysis and melting point.[182] This product is probably formed (Scheme 18) by solvolysis of the oxime (215 a) with loss of the acetyl group to form the nitrile (221) which gives the amide (222) on hydrolysis. Solvolysis of the oxime (215 a) with breakage of the bond to the 2-nitrobenzoyl group accounts for the formation of ethyl 2-nitrobenzoate which was identified by comparison with an authentic sample. Subsequent hydrolysis of this ester would yield the 2-nitrobenzoic acid also isolated. The ethyl salicylate (224), also produced, gave the characteristic purple colour with iron (III) chloride and showed an i.r. spectrum identical to that of an

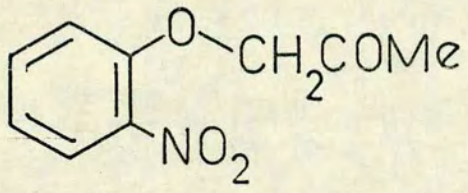
authentic sample. This product can be explained by nucleophilic displacement of the nitro group and subsequent solvolysis of the 3-acetylbenz-1,2-oxazin-4-one (223) formed. The ethyl salicylate (224) produced was further identified by benzoylation under Schotten-Baumann conditions to give ethyl O-benzoylsalicylate (225) whose m.p. corresponded well with the literature value.[183]

The attempted cyclisation of the oxime (215 b) using aqueous ethanolic sodium acetate was unsuccessful giving an essentially quantitative recovery of the starting material. The attempted cyclisation of (215 b) using aqueous ethanolic sodium carbonate gave a pale yellow oil which on trituration with ether yielded the amide (222) in low yield. T.l.c. of the oil from the trituration mother liquors showed the presence of the amide (222), ethyl 2-nitrobenzoate and ethyl salicylate (224). A high yield of benzoic acid was also isolated in this reaction which appears to follow a similar course to the cyclisation of the oxime (215 a). No attempt was made to separate the oil into its components.

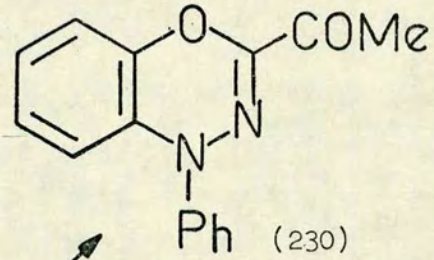
Since solvolysis is the predominant process in the base-catalysed reactions of the oximes (215 a and b), attention was next directed to a substrate which would be more resistant to solvolysis. Attempts were thus made to effect the cyclisation of 2-oximino-2'-nitrobenzoylacetonitrile (215 c). Heating this oxime under reflux in aqueous ethanolic sodium acetate gave, in addition to starting material, a neutral compound of formula $C_9H_4N_2O_2$, whose i.r. spectrum showed no hydroxyl, cyano or nitro absorption but contained a carbonyl band at 1665 cm^{-1} [compare (215 c) which shows carbonyl absorption at 1695 cm^{-1}]. This neutral product is assigned the 3-cyanobenz-1,2-oxazin-4-one structure (226) on the basis of its i.r. spectrum and by analogy with the hydrazone cyclisations [(181)→(182)]. In the analogous



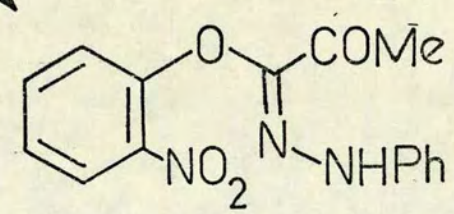
(227)



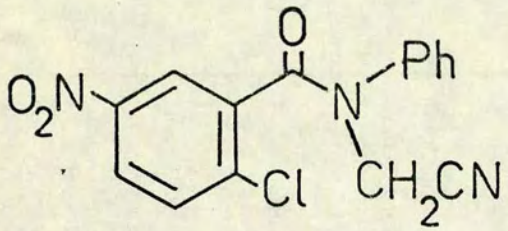
(228)



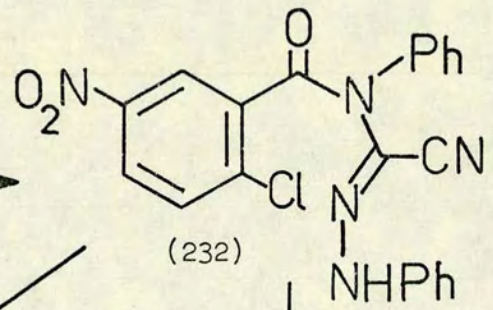
(230)



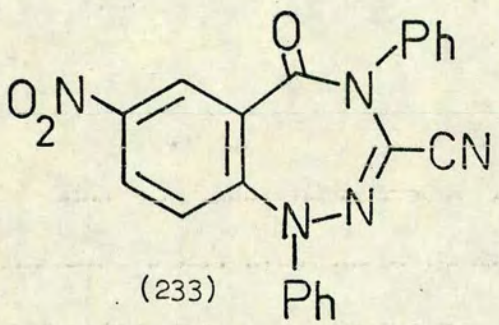
(229)



(231)

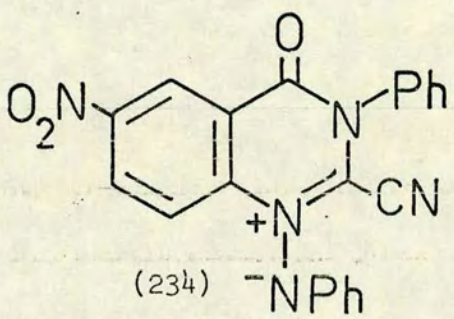


(232)



(233)

or

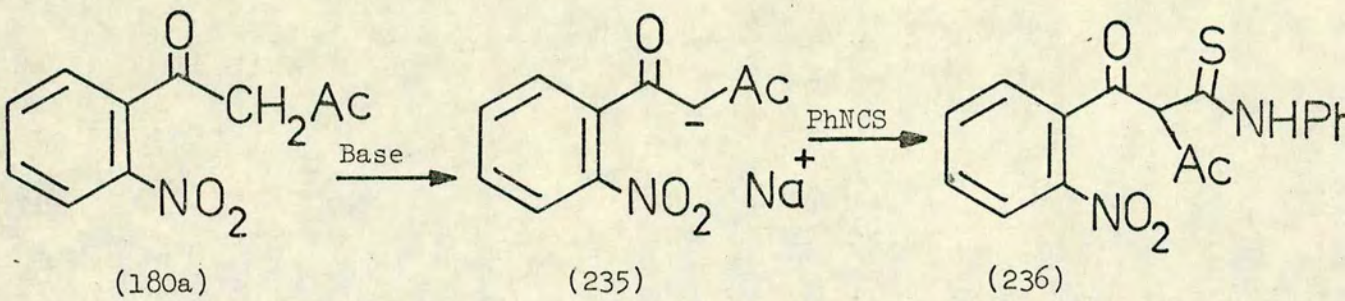


(234)

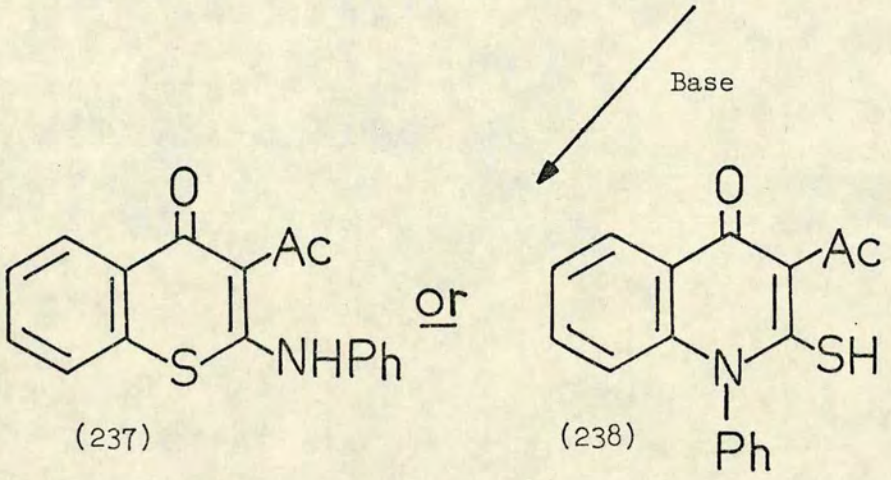
cyclisations of the hydrazones (181 a-g), the 2-nitrobenzoyl carbonyl band was generally lowered on cyclisation and this is also the case for the cyclisation of the oxime (215c). The nitrile absorption in the product (226) is presumably too weak to appear in the i.r. spectrum. The i.r. spectrum of the cyanocinnolinone (182e) likewise lacks cyano absorption. The relatively low carbonyl band at 1665 cm^{-1} is more consistent with a six-membered ring carbonyl group than the five-membered ring carbonyl group of the isomeric isatogen structure (227) since the carbonyl band in isatogens is typically at 1700-1725 cm^{-1}.[184] The oxime (215c) was also successfully cyclised by heating under reflux with piperidine in ethanol giving, in addition to starting material, the benz-1,2-oxazin-4-one (226) in moderate yield. The attempted cyclisation of (215c) by stirring at room temperature with sodium ethoxide in ethanol was unsuccessful yielding an essentially quantitative recovery of the starting material.

C. Miscellaneous Attempted Intramolecular Displacements of Aromatic Nitro Groups.

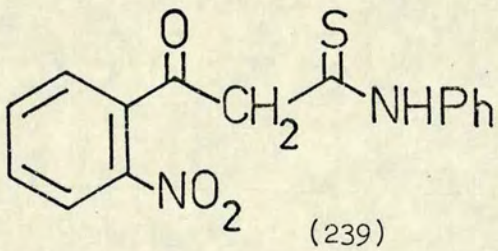
With a view to extending the scope of such cyclisation reactions, attempts were made to synthesise the hydrazones (229) and (232) by coupling benzenediazonium chloride with 2'-nitrophenoxyacetone (228) and the N,N-disubstituted benzamide (231) respectively. If these coupling reactions and the subsequent cyclisations were successful, the products would be a benz-1,3,4-oxadiazine (230) and a benzo[f]-1,2,4-triazepine (233). It was of particular interest to study the base-catalysed cyclisation of the hydrazone (232) since this would involve the formation of a seven-membered ring. Alternatively, cyclisation of (232) might occur in a sterically more favourable manner to give the



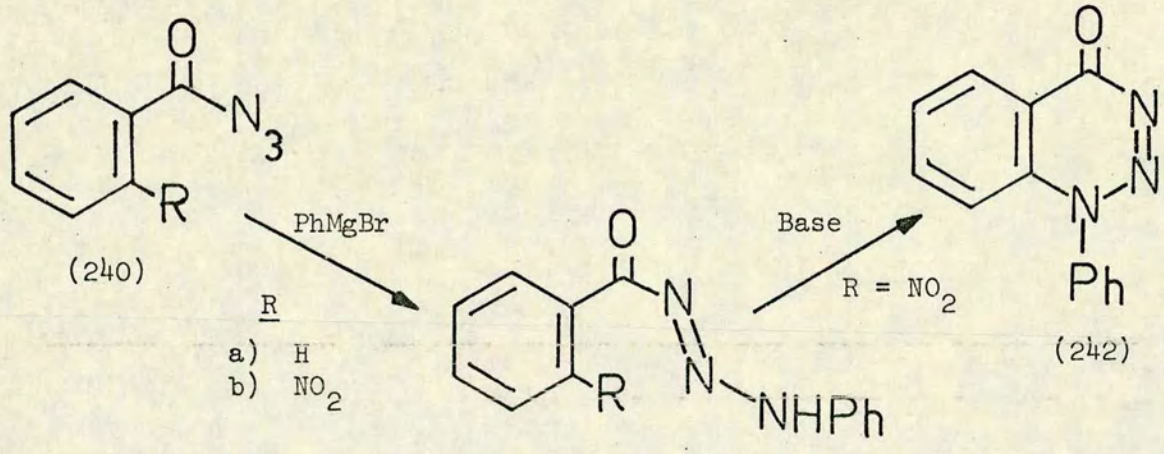
(180a) (235) (236)



(237) (238)



(239)



(240)

R

a) H
b) NO_2

(241) (242)

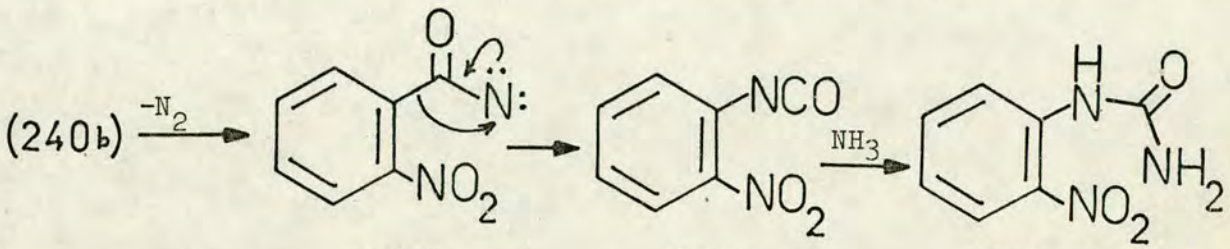
isomeric six-membered N-iminoquinazoline betaine (234).

In practice, the attempted coupling of the readily available[185] 2'-nitrophenoxyacetone with benzenediazonium chloride in the presence of sodium acetate was unsuccessful giving a 77% recovery of the starting material. Repetition of this reaction using sodium ethoxide as the catalyst resulted in the decomposition of the starting material and only multi-component mixtures were obtained. The reaction of benzenediazonium chloride with the N,N-disubstituted benzamide (231)[186] in the presence of sodium acetate was also unsuccessful giving a good recovery of the starting material.

In a further attempt to extend the scope of cyclisations involving nitro group displacement, the synthesis of the thioamide (236) was investigated. It was hoped that base-catalysed cyclisation of this compound might occur with displacement of the nitro group by either the sulphur or nitrogen centre in the side-chain thus providing a route to the heterocycles (237) and (238). In practice attempts to synthesise (236) by the addition of 2'-nitrobenzoylacetone (180a) or the derived carbanion (235) to phenylisothiocyanate were unsuccessful. Thus the free compound (180a) failed to react with phenylisothiocyanate in refluxing toluene and reaction of the sodium salt (235) in dimethylformamide as solvent gave only a low yield of the deacylated product (239). This structure is assigned on the basis of analytical and spectral data. The mass spectrum of (239) indicated a molecular weight of 300 and its i.r. spectrum contained bands at 3220, 1635 and 1540 and 1365 cm^{-1} due to NH, carbonyl and nitro absorption respectively.

The reaction of benzoylazide (240a) with phenylmagnesium bromide is known[187] to afford the triazene (241a). Since the corresponding 2-nitrobenzoyltriazene (241b) could conceivably undergo base-catalysed

cyclisation to the benzo-1,2,3-triazine (242), it was of interest to study its similar preparation from 2-nitrobenzoylazide (240b)[188] and phenylmagnesium bromide. However the only identifiable product of this reaction, formed in low yield, was 2-nitrophenylurea (245)[189] which is explicable as a product of the decomposition of the azide (240b) to the acyl nitrene (243) followed by rearrangement to the



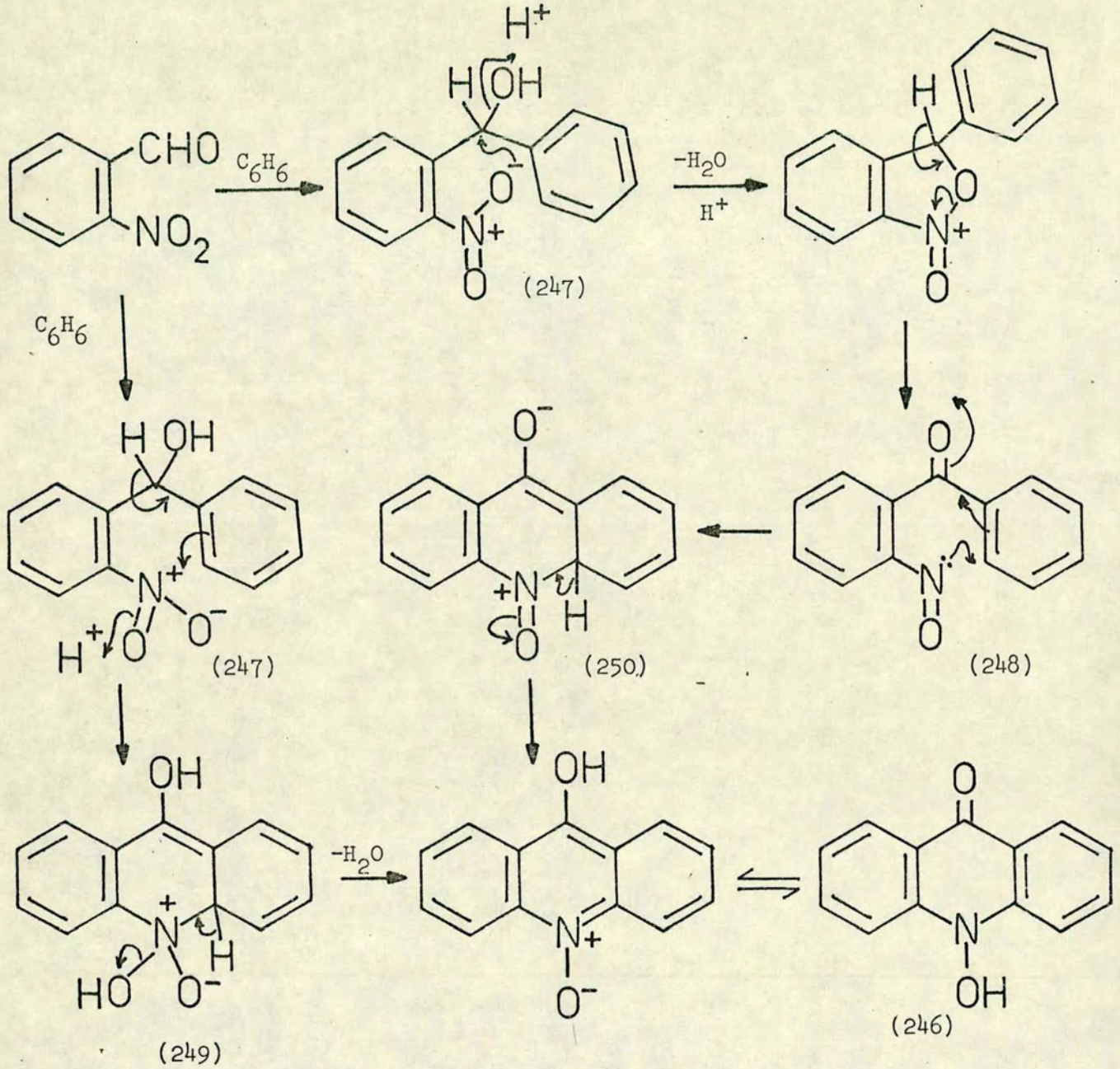
(243) (244) (245)

isocyanate (244) and reaction with ammonia (derived from the ammonium chloride used in the work up).

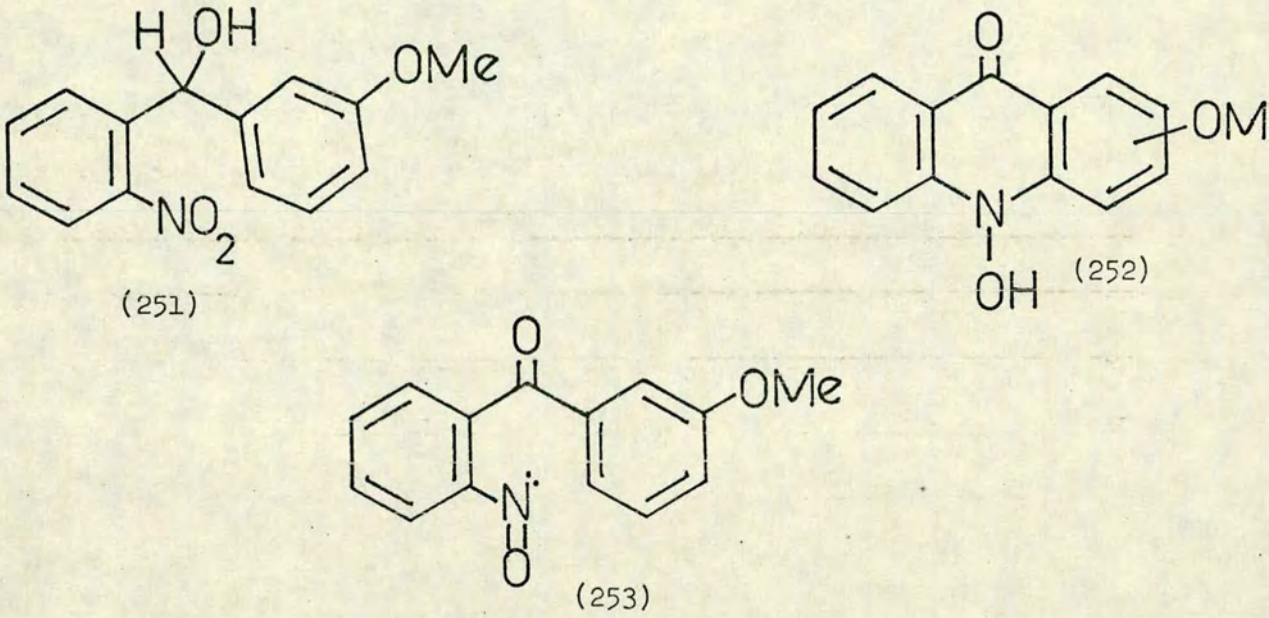
2. Miscellaneous Attempted Cyclisations involving Ortho-Nitro Groups.

Because of a general interest in the acylation reactions of heterocyclic N-oxides and N-hydroxy compounds which will be discussed in detail later (cf. Chapter 4), attempts were made to develop new syntheses for a variety of such substrates.

The condensation of 2-nitrobenzaldehyde with benzene in concentrated sulphuric acid gives in addition to anthranils (see Chapter 1) a low yield of N-hydroxyacridone (246)[190] whose formation can be rationalised by either of the mechanisms shown in Scheme 19. Internal oxidation-reduction of the intermediate benzhydrol (247) could give 2-nitrosobenzophenone (248) which could undergo cyclisation involving the nitroso group as shown (Scheme 19) to give the N-hydroxy compound (246). Alternatively, internal nucleophilic attack on the nitro group could explain the formation of (246) via the intermediate (249). This

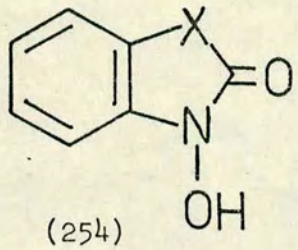

CHO
NO2
C6H6
H+
H OH
(247)
-H2O
H+
C6H6
H OH
(247)
O-
(250)
(248)
OH
-H2O
OH
O
N
OH
(246)
(249)

Scheme 19

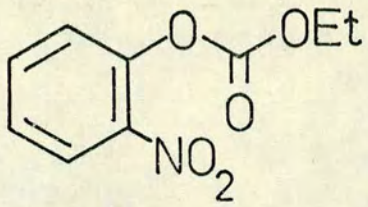

H OH
OMe
NO2
(251)
O
OM
N
OH
(252)
O
OMe
N
O
(253)

latter mechanism would be facilitated by the presence of electron-donating groups in the benzene ring which acts as the nucleophile. The presence of electron-donating groups in this ring would,on the other hand, hinder the nucleophilic substitution [(248)⟶(250)] postulated in the former mechanism. Thus, an attempt was made to synthesise the benzhydrol (251) in order to investigate the mechanism of this cyclisation and also to synthesise the corresponding N-hydroxy-acridones(252) which would be of interest in their own right since N-hydroxyacridones are practically unknown.

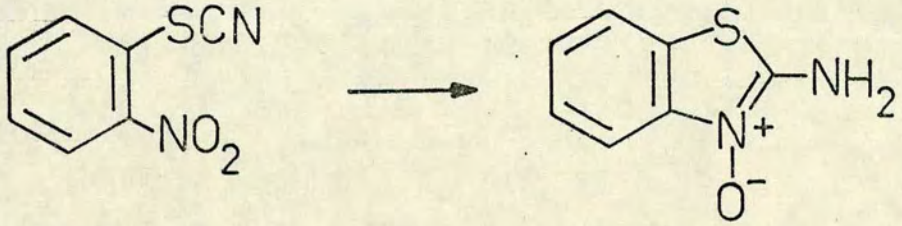
The 3'-methoxybenzhydrol (251) was synthesised in good yield by the reaction at -70° of 2-nitrobenzaldehyde with 3-methoxyphenylmagnesium bromide. However, attempts to convert (251) into the desired nitroso-compound (253) were unsuccessful. Thus, the reaction of (251) with tosyl chloride in pyridine, which had proved successful in the formation of (248) from the benzhydrol (247),[50] gave an oil which was shown by t.l.c. to consist mainly of the starting benzhydrol (251). Conversely, stirring (251) in polyphosphoric acid at 50° caused extensive decomposition with the formation of multi-component mixtures. The room temperature reaction of (251) in 98% formic acid, which was also successful for the preparation of (248),[50] gave a small amount of a solid whose i.r. spectrum contained a band at 1675 cm^{-1}. The mass spectrum of the product indicated a molecular weight of 241 and the ^{1}H n.m.r. spectrum showed signals due to eight aromatic protons and a single methoxyl group. The solid gave a green solution when dissolved in chloroform. All of these facts suggest that the solid is the nitroso ketone (253) but there was insufficient material for further characterisation. The remainder of the material recovered from this reaction was a red oil which was shown by t.l.c. to be an inseparable six component mixture. The reaction of the benzhydrol (251)



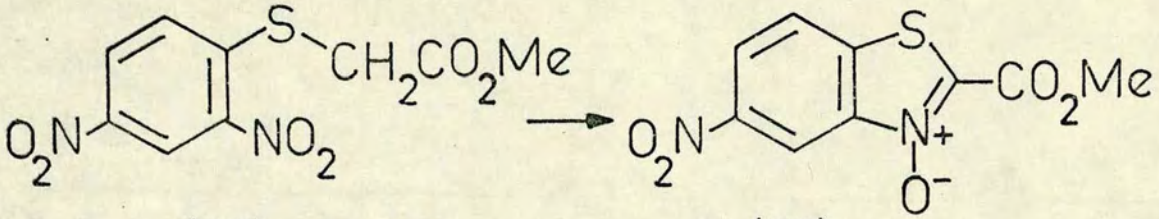
(254)



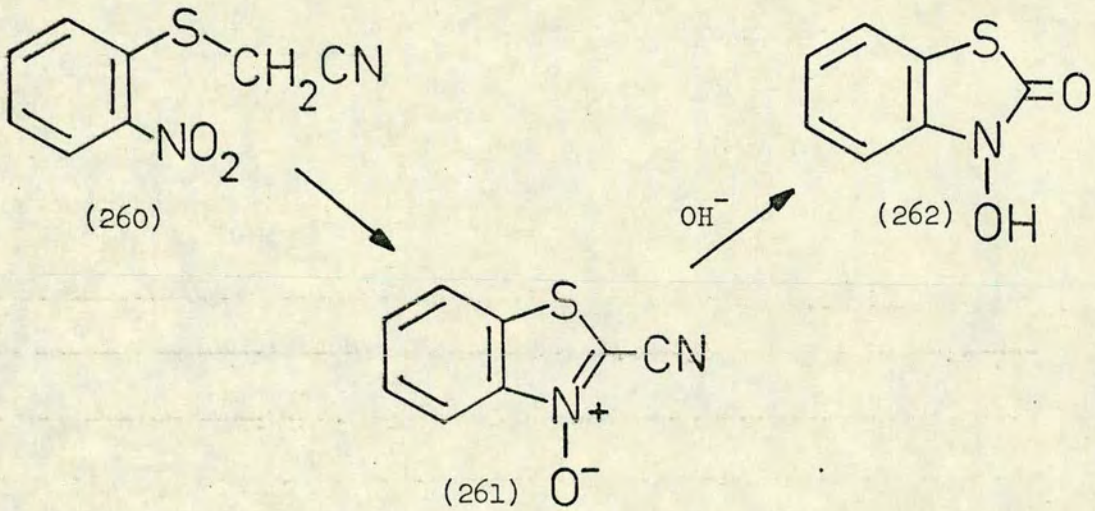
(255)



(256) (257)



(258) (259)



(260) (261) (262)

with boron trifluoride in ether gave a dark green intractable gum from which no identifiable material could be obtained.

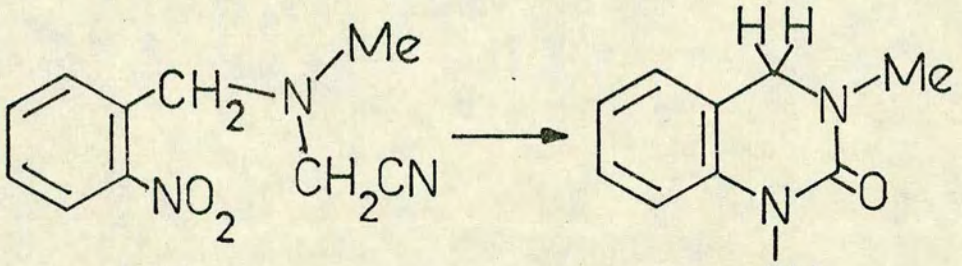
N-Hydroxybenzoxazolone (254; X = O) and N-hydroxybenzthiazolone (254; X = S) are of interest since the analogous N-hydroxybenzimidazolones (254; X = N-R) undergo nucleophilic substitution in the benzene ring under acylation conditions.[191] Attempts were therefore made to synthesise N-hydroxybenzoxazolone (254; X = O) by reductive cyclisation of the known ethyl 2-nitrophenylcarbonate (255).[192] Catalytic hydrogenation of (255) over 10% palladium charcoal gave a red solid which was shown by t.l.c. to be a three component mixture and gave a deep red colour in the presence of iron (III) chloride, typical of N-hydroxy compounds. Crystallisation failed to resolve the mixture as did dry-column chromatography. Reduction of (255) using sodium borohydride and 10% palladium charcoal[10] gave a neutral oil which was shown by t.l.c. to be a multi-component mixture consisting mainly of starting material. 2-Aminophenol[193] identified by acetylation to 2-(acetylamino)phenol[193] was also isolated in this reaction.

2-Aminobenzthiazole 3-oxide (257) is reported[194] to be formed by reductive cyclisation of 2-nitrothiocyanatobenzene (256).[195] N-Hydroxybenzthiazolone (254; X = S) might thus be available by diazotisation of (257) and subsequent hydrolysis of the resulting diazonium salt. However, the preparation of the N-oxide (257) as described in the literature could not be repeated. The attempted hydrogenation of (256) in ethanol or glacial acetic acid over 10% palladium charcoal gave an essentially quantitative recovery of the starting material. The attempted hydrogenation of (256) in ethanol over Raney-Nickel (type W4) under three or five atmospheres pressure for twenty hours also gave mainly the starting material, together with small quantities of an amphoteric solid which gave a green-blue colour in the presence of iron (III) chloride, typical

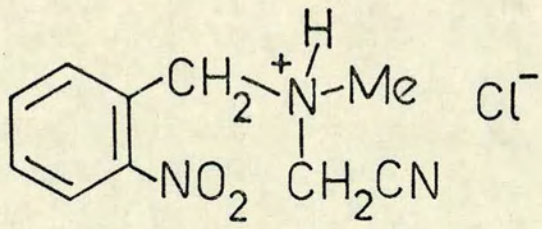
of heteroaromatic N-oxides bearing a 2-amino group. This behaviour in conjunction with the melting-point and i.r. spectrum suggests that this solid is the reported 2-aminobenzthiazole 3-oxide (257).[194] Acetylation of the solid gave a product whose melting point compared well with that reported for N-acetyl-2-aminobenzthiazole 3-oxide.[194] The i.r. and ^{1}H n.m.r. spectra of the acetylated compound are also consistent with this assignment. It would appear that (257) is being formed but only in very low yield. Repetition of the hydrogenation using more active Raney-Nickel (type W6) again gave mostly starting material together with an intractable yellow gum. None of the N-oxide (257) was isolated in this case.

Since catalytic hydrogenation was unsuccessful, chemical reduction of the nitro group in (256) was attempted. It had been reported[194] that the N-oxide (257) was also formed by reduction of (256) using either ammonium sulphide or zinc and ammonium chloride. In the present work, reduction of (256) using ethanolic ammonium sulphide gave a poor recovery of the starting material and the remainder of the material isolated was a brown intractable oil which yielded no identifiable material. Reduction of (256) with zinc dust and ammonium chloride gave an oil which afforded a moderate yield of starting material on trituration with ether. The remainder of the material in this reaction was shown by t.l.c. to be a multi-component mixture. Since it had proved impossible to repeat this literature work, the problem of the synthesis of N-hydroxybenzthiazolone (254; X = S) was approached from a different direction.

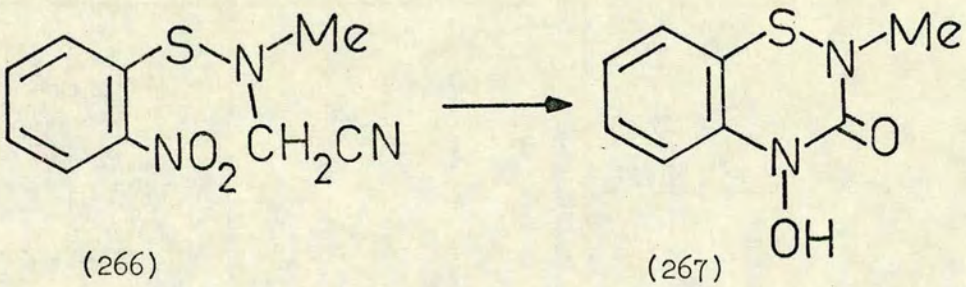
A recent report[196] of the formation of the benzthiazole 3-oxide (259) by triethylamine-catalysed cyclisation of the phenylthioacetic ester (258) suggested that cyclisation of 2-nitrophenylthioacetonitrile (260) might give 2-cyanobenzthiazole 3-oxide (261) which might in turn be converted by base into the required N-hydroxy compound (262).



(263) (264)



(265)



(266) (267)

2-Nitrophenylthioacetonitrile (260)[197] was prepared by the reaction of chloroacetonitrile with 2-nitrothiophenolate ion (generated *in situ* by the reduction of 2,2'-dinitrodiphenyldisulphide with glucose). The attempted cyclisation of (260) by heating under reflux with triethylamine in ethanol or with aqueous ethanolic sodium acetate gave an essentially quantitative recovery of the starting material. In contrast, heating (260) under reflux in aqueous ethanolic sodium carbonate solution gave only multi-component mixtures. Repetition of this reaction at room temperature gave a 50% recovery of the starting material, plus material shown by t.l.c. to be a multi-component mixture. The room temperature reaction of (260) with ethanolic sodium ethoxide gave a small quantity of 2,2'-dinitrodiphenyldisulphide. Again, the remainder of the recovered material was shown to be a multi-component mixture containing more of the disulphide. The formation of the disulphide indicates that the starting material is cleaving under the strongly basic reaction conditions to give the 2-nitrothiophenolate anion which is readily oxidised to the disulphide on acidification.

Because of an interest in the reactions of *N*-hydroxyquinazolines (see Chapter 4), attempts were also made to synthesise the quinazoline (264) and the closely related *N*-hydroxythiadiazine (267).

The condensation of 2-nitrobenzyl chloride with *N*-methylaminoacetonitrile in ethyl methyl ketone in the presence of solid sodium bicarbonate gave a three component mixture which was separated by column chromatography to give the starting 2-nitrobenzyl chloride and an orange oil. The ^{1}H n.m.r. spectrum of the latter supported its formulation as *N*-methyl-*N*-(2-nitrobenzyl)aminoacetonitrile (263) which was further characterised as its hydrochloride (265). The third component of the mixture was an unidentified red oil. The ^{1}H n.m.r. spectrum of the hydrochloride (265) showed signals due to four aromatic protons, one

methylene group, one N-methyl group and two broad singlets at τ 4.98 and τ 5.04 integrating for one proton each. These latter signals arise from the non-equivalence of the benzylic protons due to restricted rotation about the ArC-N bond. This behaviour has also been observed in other N-benzyl compounds (see Chapter 4, p.141). The mass spectra of both the oil (263) and the hydrochloride (265) show a parent ion peak at 204 mass units whereas the molecular weight of the amine (263) is 205. However, both the i.r. and ^{1}H n.m.r. spectra of the hydrochloride (265) and its elemental analysis are consistent with the proposed structure.

The attempted cyclisation of the hydrochloride (265) by heating under reflux in aqueous ethanolic sodium carbonate solution gave a good yield of the free amine (263) as a low-melting crystalline solid which could not be crystallised for further characterisation. No cyclisation had taken place. Stirring the hydrochloride (265) in ethanolic sodium ethoxide at room temperature gave very dark oils whose i.r. spectra showed the presence of a nitro group (bands at 1540 and 1365 cm^{-1}). Thus, only decomposition of the starting material had taken place and there was no evidence of the desired cyclisation.

N-Cyanomethyl-N-methyl-2-nitrophenylsulphenamide (266) was prepared in moderate yield by the condensation of 2-nitrophenylsulphenyl chloride and N-methylaminoacetonitrile hydrochloride in dry acetone in the presence of solid sodium bicarbonate. A yellow oil was obtained which was separated by column chromatography to give unreacted 2-nitrophenylsulphenyl chloride (14%), the sulphenamide (266) (45%) and an unidentified yellow solid (12%). The sulphenamide (266) was identified by its i.r. spectrum (which contains nitro group absorption at 1520 and 1345 cm^{-1}), its mass spectrum (which exhibits a parent ion at 223 mass units), its elemental analysis and its ^{1}H n.m.r. spectrum (which shows signals due to an N-methyl

group, a methylene group and four aromatic protons). The aromatic signals in the latter spectrum were sufficiently spread out to permit the assignment of the individual aromatic protons. The unidentified yellow solid was shown by its mass spectrum and elemental analysis to have the molecular formula, $C_{18}H_{16}N_4O_4S_2$. Its i.r. spectrum showed the presence of a nitro group (bands at 1525 and 1345 cm^{-1}) while its ^1H n.m.r. spectrum contained signals due to aromatic protons at τ 1.70-1.87 and 2.30-2.83 and three singlets centred at τ 5.76, 6.89 and 7.53. No structure could be found to fit these data.

The attempted cyclisation of the sulphenamide (266) using ethanolic sodium ethoxide yielded, on work up, a neutral brown intractable gum. The remainder of the recovered material was an acidic brown gum which yielded an unidentified pale brown solid whose i.r. spectrum showed the presence of a nitro group (1525 and 1340 cm^{-1}) and whose ^1H n.m.r. spectrum contained signals due to aromatic protons and the protons of an ethyl group as well as a one proton singlet at τ 3.51. No structure could be found to fit these data but the presence of the nitro group shows that cyclisation has not occurred.

CHAPTER THREE

EXPERIMENTAL

PART 1

A. 1-Phenylcinnolin-4(1H)-ones

1. The Preparation of 2- and 3-Nitrobenzoyl Chlorides.

(i) 2-Nitrobenzoyl chloride was prepared as described by Taylor and Eckroth[198] (95%) and had b.p. 99-110°/0.30 mm (lit.,[198] 120-125°/0.40 mm).

(ii) 3-Nitrobenzoyl chloride was prepared as for 2-nitrobenzoyl chloride (94%) and had b.p. 96-101°/0.05 mm (lit.,[199] 154-158°/18.0 mm).

2. The Preparation of Ethyl 2'- and 3'-Nitrobenzoylacetoacetates.

(i) Ethyl 2'-nitrobenzoylacetoacetate was obtained by condensing 2-nitrobenzoyl chloride with ethyl acetoacetate in the presence of sodium ethoxide, using (a) the method of Needham and Perkin[156] (50%) or (b) the method of Bülow and Hailer[155] (68%), as a brown oil, $\tau(CDCl_3)$ 1.82 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-3'), 2.22-2.55 (2H, m, ArH), 2.71 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-6'), 6.14 (2H, q, J 7 Hz, $\underline{CH_2}$-CH_3), 7.47 (3H, s, COMe) and 9.20 (3H, t, J 7 Hz, CH_2-$\underline{CH_3}$).

(ii) Ethyl 3'-nitrobenzoylacetoacetate was prepared as described by Bülow and Hailer[155] (87%) and had m.p. 64-73° (lit.,[155] 74-75°), $\tau(CDCl_3)$ 1.43 (1 unit, m, ArH), 1.53-1.74 (3 units, m, ArH), 1.82-1.97 (1 unit, m, ArH), 2.10-2.49 (3 units, m, ArH), 5.92 (2 units, q, J 7 Hz, $\underline{CH_2}$-CH_3), 5.97 (2 units, q, J 7 Hz, $\underline{CH_2}$-CH_3), 7.54 (3 units, s, COMe), 7.83 (3 units, s, COMe), 9.05 (3 units, t, J 7 Hz, CH_2-$\underline{CH_3}$) and 9.08 (3 units, t, J 7 Hz, CH_2-$\underline{CH_3}$).

3. The Preparation of Ethyl 2'-Nitrobenzoylbenzoylacetate.

Ethyl 2'-nitrobenzoylbenzoylacetate was prepared by condensing

2-nitrobenzoyl chloride with ethyl benzoylacetate in the presence of sodium ethoxide using the method of Needham and Perkin[156] (60%) and had m.p. 78-85° (lit.,[8] 88°).

4. The Preparation of the β-Diketones (180a,b) and (205).

The β-diketones (180a,b) and (205) were prepared from the corresponding acyl nitrobenzoylacetic esters by hydrolysis and decarboxylation in hot aqueous dilute sulphuric acid using the method of Needham and Perkin.[156]

(i) Ethyl 2'-nitrobenzoylacetoacetate gave 2'-nitrobenzoylacetone (180a) (53%), m.p. 53-58° (lit.,[156] 55°), τ($CDCl_3$) 2.00-2.14 (1H, m, H-3'), 2.24-2.53 (3H, m, ArH), 4.17 (1H, s, olefinic CH) and 7.87 (3H, s, Me).

(ii) Ethyl 3'-nitrobenzoylacetoacetate gave 3'-nitrobenzoylacetone (205) (33%), m.p. 108-113° (lit.,[155] 115°), τ($CDCl_3$) 1.32 (1H, t, J_{meta} 2 Hz, H-2'), 1.65 (1H, dt, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-4'), 1.80 (1H, dt, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-6'), 2.40 (1H, t, J_{ortho} 8 Hz, H-5'), 3.75 (1H, s, olefinic CH) and 7.76 (3H, s, Me).

(iii) Ethyl 2'-nitrobenzoylbenzoylacetate gave 2'-nitrodibenzoylmethane (180b) (80%), m.p. 114-117° (lit.,[8] 116°).

5. The Preparation of Ethyl 2'-Nitrobenzoylacetate (180c).

The ester (180c) was prepared by the method of Wibberly et al.[154] from the sodium salt of ethyl 2'-nitrobenzoylacetoacetate as a slightly oily brown solid (31%), m.p. <30° (lit.,[200] 36°), τ($CDCl_3$) 1.86 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-3'), 2.13-2.54 (3H, m, ArH), 5.86 (2H, q, J 7 Hz, $\underline{CH_2}$-CH_3), 6.14 (2H, s, CH_2) and 8.79 (3H, t, J 7 Hz, CH_2-$\underline{CH_3}$). The ^1H n.m.r. spectrum also showed a minor trace (<10%) of starting material (peak at τ 7.47 - COMe).

Acidification of the aqueous filtrate from the purification of (180c) and extraction with chloroform gave starting material (24%), identical (i.r. and ^{1}H n.m.r. spectra) to an authentic sample.

6. The Preparation of 2'-Nitroacetophenone (180h).

2'-Nitroacetophenone (180h) was prepared from 2-nitrobenzoyl chloride and diethyl malonate by the method of Reynolds and Hauser[162] (84%) and had b.p. 158-159°/13 mm (lit.,[162] 158-159°/16 mm).

7. The Preparation of 2-Bromo-2'-nitroacetophenone (180i).

2-Bromo-2'-nitroacetophenone (180i) was prepared from 2'-nitroacetophenone by the method of Gevekoht[161] (75%) and had m.p. 54-55° (lit.,[161] 55-56°), $\nu_{max.}$ 1715(CO) and 1540 and 1355(NO_2) cm^{-1}.

8. The Preparation of 2'-Nitrobenzoylacetonitrile (180d).

2'-Nitrobenzoylacetonitrile (180d) was prepared from 2-bromo-2'-nitroacetophenone (180i) by the method of Arndt et al.[160] (85%) and had m.p. 90-95° (lit.,[160] 102°), $\nu_{max.}$ 2300w (C≡N), 1710(CO) and 1535 and 1350(NO_2) cm^{-1}.

9. The Preparation of 2'-Nitrobenzoylacetamide (180e).

A solution of 2'-nitrobenzoylacetonitrile (180d) (0.76g, 0.004 mol) in polyphosphoric acid (~6 ml) was stirred at 80° for 3h. The mixture was cooled in ice and treated with water (15 ml) to give a pale brown solid (0.50g) which was combined with a further crop (0.20g) obtained by extracting the aqueous filtrate with chloroform to give 2'-nitrobenzoylacetamide (180e) (85%), as colourless needles, m.p. 126-127° (from benzene - light petroleum), $\nu_{max.}$ 3480 and 3260 br (NH_2), 1710 and 1660(CO) and 1535 and 1350(NO_2) cm^{-1}.

Found: C,52.0%; H,4.0%; N,13.4%.

$C_9H_8N_2O_4$ requires: C,51.9%; H,3.9%; N,13.5%.

10. The Preparation of 2,2'-Dinitroacetophenone (180g).

(i) 1-(2'-Nitrophenyl)-2-nitroethanol (185) was prepared by the sodium methoxide-catalysed condensation of 2-nitrobenzaldehyde with nitromethane as described by Long and Troutmann[152] (66%) and had m.p. 57-59° (decomp.) [lit.,[158] 63°(decomp.)], $\nu_{max.}$ 3550(OH) and 1560, 1540 and 1355(NO_2) cm^{-1}, $\tau(CDCl_3)$ 1.88-2.58 (4H, m, ArH), 3.99 (1H, dd, J_{AC} 3 Hz, J_{AB} 9 Hz, CH_A), 5.15 (1H, dd, J_{AC} 3 Hz, J_{CB} 14 Hz, CH_CNO_2), 5.47 (1H, dd, J_{AB} 9 Hz, J_{CB} 14 Hz, CH_BNO_2) and 6.56 (1H, s, OH).

(ii) 2,2'-Dinitroacetophenone (180g) was prepared by the oxidation of 1-(2'-nitrophenyl)-2-nitroethanol (185) with potassium dichromate in concentrated sulphuric acid using the method of Canonica and Cardani[157] (75%) and had m.p. 135-139° (lit.,[157] 135°), $\nu_{max.}$ 1715(CO) and 1555, 1540, 1350 and 1335(NO_2) cm^{-1}, $\tau[(CD_3)_2CO]$ 1.65-1.79 (1H, m, H-3'), 1.99-2.23 (3H, m, ArH) and 3.89 (2H, s, CH_2).

11. The Preparation of 2-Benzenesulphonyl-2'-nitroacetophenone (180f).

2-Bromo-2'-nitroacetophenone (180i) (2.4g, 0.01 mol) and sodium benzenesulphinate dihydrate (2.1g, 0.011 mol) were heated under reflux in ethanol (50 ml) for 4h. The oily residue, obtained by evaporation of the solution, was treated with water (10 ml) and extracted with chloroform to give a yellow oil which solidified on rubbing. Crystallisation from benzene-light petroleum gave the pure 2-benzenesulphonyl-2'-nitroacetophenone (180f) (76%) as a colourless amorphous solid, m.p. 86-87°, $\nu_{max.}$ 1695(CO) and 1545 and 1350(NO_2) cm^{-1}.

Found: C,55.5%; H,3.7%; N,4.6%; S,10.5%; M^+259.

$C_{14}H_{11}NO_5S$ requires: C,55.1%; H,3.6%; N,4.6%; S,10.5%; M 305.

12. The Preparation of 2'-Nitrobenzoylacetic Acid (180j).

2'-Nitrobenzoylacetic acid (180j) was prepared from ethyl 2'-nitrobenzoylacetoacetate in concentrated sulphuric acid using the method of Overmeyer[163] (95%) and had m.p. 103-110° (lit.,[163] 117°), $\nu_{max.}$ 2680br(OH), 1720 and 1685(CO) and 1540 and 1355 (NO_2) cm^{-1}.

13. The Preparation of 1-(2'-Nitrophenacyl)pyridinium Bromide (180k).

A solution of 2-bromo-2'-nitroacetophenone (180i) (12.2g, 0.05 mol) and redistilled pyridine (10 ml, 0.125 mol) in sodium-dried ether (100 ml) left at room temperature for 7 days deposited 1-(2'-nitrophenacyl)-pyridinium bromide (180k) as a cream coloured insoluble solid (13.96g, 87%), m.p. 250-253° (decomp.). Crystallisation from aqueous ethanol gave colourless needles, m.p. 255-256° (decomp.), $\nu_{max.}$ 1715(CO) and 1540 and 1365(NO_2) cm^{-1}, $\tau[(CD_3)_2SO]$ 0.89-1.05 (2H, m, ArH), 1.12-1.31 (1H, m, ArH), 1.56-1.77 (3H, m, ArH), 1.86-2.16 (3H, m, ArH) and 3.56 (2H, s, CH_2).

Found: C,48.1%; H,3.4%; Br,24.6%; N,8.9%; M^+(cation) 243.

$C_{13}H_{11}BrN_2O_3$ requires: C,48.3%; H,3.4%; Br,24.8%; N,8.8%; M(cation) 243.

14. The Preparation of Phenacylidene Phenylhydrazones(181a-g) and (206).

A solution of benzenediazonium chloride was prepared by the dropwise addition of a solution of sodium nitrite (0.30g) in water (2.0 ml) to a stirred solution of aniline (0.36g, 0.004 mol) in aqueous 5N hydrochloric acid (2.2 ml), at 0-5°, at such a rate that the temperature did not rise above 10°. After the addition was complete, the solution was checked for an excess of nitrous acid using starch-iodide paper. The amber diazonium

salt solution was added dropwise with stirring at 10-15° to a solution of the active methylene compound (0.004 mol) and sodium acetate (0.62g) in aqueous ethanol or aqueous acetone. Stirring was continued at 10-15° for 30 min. and the insoluble solid was collected and crystallised to give the pure phenacylidene phenylhydrazone.

(i) 2'-Nitrobenzoylacetone (180a) in ethanol (15 ml) and water (4.0 ml) yielded 1-(2'-nitrophenyl)butane-1,2,3-trione 2-phenylhydrazone (181a) (97%), m.p. 108-113°. Crystallisation from ethanol gave bright yellow needles, m.p. 121-122°, $\nu_{max.}$ 1655 and 1635(CO) and 1530 and 1355(NO_2) cm^{-1}.

Found: C,61.2%; H,4.2%; N,13.8%; M^+311.

$C_{16}H_{13}N_3O_4$ requires: C,61.7%; H,4.2%; N,13.5%; M 311.

(ii) 3'-Nitrobenzoylacetone (205) in ethanol (80 ml) and water (5.0 ml) yielded 1-(3'-nitrophenyl)butane-1,2,3-trione 2-phenylhydrazone (206) (90%), m.p. 192-195°. Crystallisation from glacial acetic acid gave bright yellow fibrous needles, m.p. 194-195°, $\nu_{max.}$ 1650 and 1625(CO) and 1525 and 1360(NO_2) cm^{-1}, τ(CF_3CO_2H) 1.28 (1H, d, J_{meta} 2 Hz, H-2'), 1.47 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-4'), 1.82 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-6'), 2.24 (1H, t, J_{ortho} 8 Hz, H-5'), 2.65 (5H, s, ArH) and 7.12 (3H, s, Me).

Found: C,61.6%; H,4.2%; N,13.3%; M^+311.

$C_{16}H_{13}N_3O_4$ requires: C,61.7%; H,4.2%; N,13.5%; M 311.

(iii) 2'-Nitrodibenzoylmethane (180b) in ethanol (450 ml) and water (10 ml) yielded 1-(2'-nitrophenyl)-3-phenylpropane-1,2,3-trione 2-phenylhydrazone (181b) (quantitative), m.p. 109 -114°. Crystallisation from ethanol gave bright yellow needles, m.p. 124-125°, $\nu_{max.}$ 1650 and 1630(CO) and 1540 and 1370(NO_2) cm^{-1}.

Found: C,67.1%; H,4.2%; N,11.1%; M^+373.

$C_{21}H_{15}N_3O_4$ requires: C,67.5%; H,4.1%; N,11.3%; M 373.

(iv) Ethyl 2'-nitrobenzoylacetate (180c) in ethanol (20 ml) and water (4.0 ml) yielded ethyl 2-(2'-nitrobenzoyl)-2-phenylhydrazono-acetate (181c) (80%), m.p. 114-120°, after concentration of the aqueous ethanolic solution. Crystallisation from ethanol gave bright yellow prisms, m.p. 125-126°, $\nu_{max.}$ 1660(CO) and 1540 and 1360(NO_2) cm^{-1}.

Found: C,60.1%; H,4.4%; N,12.4%; M^+341.

$C_{17}H_{15}N_3O_5$ requires: C,59.8%; H, 4.4%; N,12.3%; M 341.

(v) 2'-Nitrobenzoylacetonitrile (180d) in ethanol (25 ml) and water (5.0 ml) yielded 2-(2'-nitrobenzoyl)-2-phenylhydrazonoacetonitrile (181d) (92%), m.p. 159-161°. Crystallisation from ethanol gave bright yellow needles, m.p. 161-163°, $\nu_{max.}$ 3200w(NH), 2250w(C≡N), 1675(CO) and 1530 and 1355(NO_2) cm^{-1}.

Found: C,61.2%; H,3.4%; N,19.1%; M^+294.

$C_{15}H_{10}N_4O_3$ requires: C,61.2%; H,3.4%; N,19.0%; M 294.

(vi) 2'-Nitrobenzoylacetamide (180e) in ethanol (65 ml) and water (5.0 ml) yielded 2-(2'-nitrobenzoyl)-2-phenylhydrazonoacetamide (181e) (87%). Crystallisation from ethanol-glacial acetic acid gave bright yellow needles, m.p. 179-196° with resolidification and further melting at 270-275° (decomp.), $\nu_{max.}$ 3430 and 3240br(NH_2), 1665 and 1640(CO) and 1540 and 1360(NO_2) cm^{-1}.

Found: C,57.6%; H,3.9%; N,17.9%; M^+312.

$C_{15}H_{12}N_4O_4$ requires: C,57.7%; H,3.9%; N,17.9%; M 312.

(vii) 2-Benzenesulphonyl-2'-nitroacetophenone (180f) in ethanol (70 ml) and water (4.0 ml) yielded 2-benzenesulphonyl-2-phenylhydrazono-2'-nitroacetophenone (181f) (95%). Crystallisation from ethanol gave a mixture of bright yellow prisms and needles, m.p. 151-169°, $\nu_{max.}$ 3250w(NH), 1665(CO) and 1545 and 1355(NO_2) cm^{-1}.

Found: C,59.0%; H,3.8%; N,10.5%; S,7.9%; M^+409.

$C_{20}H_{15}N_3O_5S$ requires: C,58.7%; H,3.7%; N,10.3%; S,7.8%; M 409.

(viii) 2,2'-Dinitroacetophenone (180g) in acetone (35 ml) and water (12 ml) yielded, after concentration of the mixture, 2,2'-dinitro-2-phenylhydrazonoacetophenone (181g) (90%), m.p. 120-126°. Crystallisation from ethanol-glacial acetic acid gave bright yellow prisms, m.p. 134-135°, $\nu_{max.}$ 1630w(CO) and 1545, 1520, 1350 and 1295(NO_2) cm^{-1}.

Found: C,53.3%; H,3.3%; N,17.8%; M^+314.

$C_{14}H_{10}N_4O_5$ requires: C,53.5%; H,3.2%; N,17.8%; M 314.

(ix) 2-Bromo-2'-nitroacetophenone (180i) in ethanol (35 ml) and water (8.0 ml) gave a yellow solid (0.21g). Concentration of the filtrate and extraction into chloroform gave a dark red oil (1.06g). T.l.c. in benzene over silica showed both the solid and the oil to be at least three component mixtures with starting material as the major component. Crystallisation of the solid from benzene-light petroleum or trituration of the oil with various organic solvents failed to produce any identifiable material.

(x) 2'-Nitrobenzoylacetic acid (180j) in ethanol (10 ml) and water (15 ml) gave a deep red solution which was acidified and extracted with chloroform. The organic layer was washed with 10% w/v aqueous sodium hydroxide and evaporated to yield a dark red oil (0.97g) which could not be obtained solid. T.l.c. in chloroform over silica or alumina showed it to be at least a two component mixture which could not be separated on attempted dry-column chromatography in chloroform over alumina.

The alkaline washings were acidified and extracted with chloroform to give a red oil (0.12g) which yielded, on trituration with ether, a colourless unidentified solid (0.04g), m.p. 183-185° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1735 and 1640(CO) and 1535 and 1355(NO_2) cm^{-1}.

Found: C,56.7%; H,2.6%; N,7.4%; M^+336.

$C_9H_5NO_4$ requires: C,56.6%; H,2.6%; N,7.3%; M 191.

Evaporation of the trituration liquors gave a red oil (0.08g) which was shown by t.l.c. in chloroform over silica to be an unresolvable four component mixture.

(xi) The mixture from 1-(2'-nitrophenacyl)pyridinium bromide (180k) and sodium acetate (1.13g) in water (140 ml) (containing a solid) was basified with 10% w/v aqueous sodium hydroxide to give 1-[(2-phenylhydrazono)-2'-nitrophenacyl]pyridinium betaine (183) (quantitative), as an orange solid, m.p. 110-119° (decomp.), $\nu_{max.}$ 1565(CO) and 1525 and 1340(NO_2) cm^{-1}, τ [$(CD_3)_2SO$] 1.28 (2H, m, ArH), 1.44 (1H, m, ArH), 1.71-1.99 (3H, m, ArH), 2.11-2.44 (3H, m, ArH) and 2.75-3.19 (5H, m, ArH), M^+300, ($C_{19}H_{14}N_4O_3$ requires M 346). Treatment of the betaine (183) with aqueous 2.5N hydrochloric acid gave a yellow hydrochloride, m.p. 155-160°, $\nu_{max.}$ 3400m(NH), 1670m(CO) and 1560 and 1350(NO_2) cm^{-1}. The betaine (183) also formed a picrate as yellow prisms, m.p. 180-182° (from glacial acetic acid), $\nu_{max.}$ 1675m(CO) and 1570, 1350 and 1320(NO_2) cm^{-1}.

Found: C,51.8%; H,3.0%; N,16.8%; M^+(cation)347.

$C_{25}H_{17}N_7O_{10}$ requires: C,52.2%; H,3.0%; N,17.0%; M(cation)347.

15. The Attempted Reaction of 2'-Nitroacetophenone (180h) and 2-Bromo-2'-nitroacetophenone (180i) with Benzenediazonium Chloride.

A solution of the nitro compound (180h) or (180i) (0.004 mol) in absolute ethanol (30 ml) was treated with a solution of sodium (0.19g) in absolute ethanol (5.0 ml) and after cooling to 0° the mixture was treated dropwise with a solution of benzenediazonium chloride prepared as described in A.14 (p.58). After stirring at 0° for 30 min. the mixture was evaporated, treated with water (15 ml) and extracted with chloroform (extract A).

(i) Extract A in the reaction with 2'-nitroacetophenone (180h)

yielded a deep red intractable oil (0.35g). Acidification of the aqueous layer and extraction with chloroform gave another dark red intractable oil (0.38g). T.l.c. of both oils in chloroform or chloroform-methanol over silica showed them to be multi-component mixtures which were not investigated further.

(ii) Extract A in the reaction of 2-bromo-2'-nitroacetophenone (180i) yielded a deep red intractable oil (0.51g). Acidification of the aqueous layer and extraction with chloroform gave another dark red intractable oil (0.60g). T.l.c. of both oils in chloroform over silica showed them to be multi-component mixtures which were not investigated further.

16. The Preparation of 3-Substituted-1-phenylcinnolin-4(1H)-ones (182a-h) by the Base-catalysed Cyclisations of the Hydrazones (181a-g).

The hydrazone (0.002 mol) in ethanol was heated under reflux with (a) aqueous N sodium carbonate solution (5.0 ml) or (b) aqueous N sodium acetate solution (5.0 ml) for 1-2h. The solution became red in colour after a few minutes and gradually lightened to colourless or pale yellow when the reaction was complete. The product was isolated by evaporation of the reaction mixture and trituration of the residue with water (10 ml).

(i) (a) Heating the hydrazone (181a) with aqueous sodium carbonate solution for 1h in ethanol (20 ml) gave a pale brown solid whose t.l.c. in chloroform over silica showed it to be a two component mixture. Wet-column chromatography in ether-toluene (1:1) over alumina gave 3-acetyl-1-phenylcinnolin-4(1H)-one (182a) as colourless fibrous needles (89%), m.p. 164-165° (from benzene-light petroleum),

$\nu_{max.}$ 1690 and 1635(CO) cm^{-1}, $\tau(CDCl_3)$ 1.58 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.25-2.55 (7H, m, ArH), 2.67-2.81 (1H, m, ArH) and 7.36 (3H, s, Me).

Found: C,72.8%; H,4.8%; N,11.0%; M^+264.

$C_{16}H_{12}N_2O_2$ requires: C,72.7%; H,4.6%; N,10.6%; M 264.

The other component of the mixture could not be recovered from the column.

(b) Heating the hydrazone (181a) in ethanol (20 ml) with aqueous sodium acetate solution for 1h gave a quantitative recovery of the starting material, identical (m.p. and i.r. spectrum) to an authentic sample.

The cinnolinone (182a) on heating under reflux with hydroxylamine hydrochloride and sodium acetate in ethanol formed a monoxime (191) as pale yellow needles (97%), m.p. 258-262° (decomp.) (from dimethylformamide-water), $\nu_{max.}$ 3200br(OH) and 1630(CO) cm^{-1}, $\tau(CF_3CO_2H)$ 1.32 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 1.78-2.44 (8H, m, ArH) and 7.19 (3H, s, Me).

Found: C,68.8%; H,4.8%; N,15.5%; M^+279.

$C_{16}H_{13}N_3O_2$ requires: C,68.8%; H,4.7%; N,15.4%; M 279.

(ii) Heating the hydrazone (181b) under reflux with aqueous sodium carbonate solution in ethanol (50 ml) for 1h gave 3-benzoyl-1-phenylcinnolin-4(1H)-one (182b) as colourless plates (83%), m.p. 181-183° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1660 and 1620(CO) cm^{-1}.

Found: C,77.0%; H, 4.3%; N,8.6%; M^+326.

$C_{21}H_{14}N_2O_2$ requires: C,77.3%; H,4.3%; N,8.6%; M 326.

(iii) Heating the hydrazone (181c) under reflux with aqueous sodium carbonate solution in ethanol for 1h gave 3-ethoxycarbonyl-1-phenylcinnolin-4(1H)-one (182c) as colourless prisms (72%), m.p. 151-152° (from ethanol-water), $\nu_{max.}$ 1725 and 1635(CO) cm^{-1}, $\tau(CDCl_3)$ 1.57

(1H, m, ArH), 2.34-2.64 (7H, m, ArH), 2.84 (1H, m, ArH), 5.55 (2H, q, J 7 Hz, $\underline{CH_2}$-CH_3) and 8.60 (3H, t, J 7 Hz, CH_2-$\underline{CH_3}$).

Found: C,69.8%; H,4.8%; N,9.7%; M^+294.

$\underline{C_{17}H_{14}N_2O_3}$ requires: C,69.4%; H,4.8%; N,9.5%; M 294.

After washing with chloroform to remove a small quantity of the starting material (5%), identical (i.r. spectrum) to an authentic sample, the aqueous mother liquors were acidified to give 1-phenylcinnolin-4(1H)-one-3-carboxylic acid (182d) as colourless fibrous needles (19%), m.p. 274-275° (lit.,[153] 275°), $\nu_{max.}$ 2750br(OH) and 1740 and 1590(CO) cm^{-1}, T[$(CD_3)_2SO$] 1.67 (1H,dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.01-2.39 (2H, m, ArH), 2.32 (5H, s, ArH) and 2.72 (1H, d, J_{ortho} 8 Hz, H-8).

Found: C,67.3%; H,3.7%; N,10.7%; M^+266.

$\underline{C_{15}H_{10}N_2O_3}$ requires: C,67.7%; H,3.8%; N,10.5%; M 266.

(iv) (a) Heating the hydrazone (181d) under reflux with aqueous sodium carbonate solution in ethanol (30 ml) for 48h gave 1-phenylcinnolin-4(1H)-one-3-carboxamide (182f) as colourless prisms (65%), m.p. 292-294° (decomp.) (from glacial acetic acid-water), $\nu_{max.}$ 3370 and 3220 (NH_2) and 1680 and 1645(CO) cm^{-1}.

Found: C,67.5%; H,4.3%; N,15.6%; M^+265.

$\underline{C_{15}H_{11}N_3O_2}$ requires: C,67.9%; H,4.2%; N,15.8%; M 265.

The filtrate was evaporated and the residue was treated with water (10 ml) and washed with chloroform. Acidification of the aqueous layer yielded the carboxylic acid (182d) as colourless needles (25%), m.p. 273-275° (lit.,[153] 275°), identical (m.p. and i.r. spectrum) to the sample prepared as described in (iii) above.

(b) Heating the hydrazone (181d) under reflux with aqueous sodium acetate solution in ethanol (30 ml) for 40h gave 3-cyano-1-phenylcinnolin-4(1H)-one (182e) as colourless plates (91%), m.p. 223-224° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1645 (CO) cm^{-1}.

Found: C,72.7%; H,3.6%; N,17.0%; M^+247.

$C_{15}H_9N_3O$ requires: C,72.9%; H,3.7%; N,17.0%; M 247.

(c) Heating the hydrazone (181d) under reflux with aqueous sodium carbonate solution in ethanol (30 ml) for 2h gave an orange salt (0.66g) which was dissolved in water, with filtration to remove a small quantity of the cyanocinnolinone (182e) (10%), identical (i.r. and mass spectrum) to a sample prepared as in (iv) (b), above. Acidification of the aqueous filtrate gave starting material, identical (i.r. spectrum) to an authentic sample, which was combined with a second crop (total - 0.50g, 85%) obtained by acidification of the original aqueous mother liquors.

(v) Heating the hydrazone (181e) under reflux with aqueous sodium carbonate solution in ethanol (50 ml) for 1.75h, followed by ice-cooling gave the amide (182f) as colourless prisms (98%), m.p. 283-289° (decomp.), identical (m.p. and i.r. spectrum) to the sample prepared as described in (iv) (a) above.

(vi) Heating the hydrazone (181f) under reflux with aqueous sodium carbonate solution in ethanol (60 ml) for 1h, followed by ice-cooling gave 3-benzenesulphonyl-1-phenylcinnolin-4(1H)-one (182g) as colourless plates, (75%), m.p. 275-276° (from glacial acetic acid-dimethylformamide), $\nu_{max.}$ 1635(CO) cm^{-1}.

Found: C,66.1%; H,3.9%; N,7.6%; M^+362.

$C_{20}H_{14}N_2O_3S$ requires: C,66.3%; H,3.9%; N,7.7%; M 362.

(vii) (a) Heating hydrazone (181g) under reflux with aqueous sodium carbonate solution in ethanol (45 ml) for 1h and diluting the mixture with water afforded no solid. Extraction of the mixture with chloroform and trituration of the resultant dark red oil with ether-light petroleum gave 3-nitro-1-phenylcinnolin-4(1H)-one (182h) as pale

yellow prisms (42%), m.p. 189-190° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1660(CO) and 1540 and 1320(NO_2) cm^{-1}.

Found: C,62.7%; H,3.2%; N,15.6%; M^+267.
$C_{14}H_9N_3O_3$ requires: C,62.9%; H,3.4%; N,15.7%; M 267.

Evaporation of the trituration liquors yielded a dark red oil (0.32g) whose t.l.c. in chloroform over silica showed it to be a multi-component mixture containing traces of the starting material and the cinnoline (182h). Acidification of the aqueous mother liquors and extraction with chloroform also gave a red oil (0.10g). Trituration of the red oils with a variety of organic solvents failed to produce any identifiable material.

(b) The hydrazone (181g) was heated under reflux with aqueous sodium acetate solution in ethanol for 1h. Evaporation of the mixture, treatment with water (10 ml) and extraction with chloroform gave a dark red oil which on trituration with ether-light petroleum gave the nitro compound (182h) (37%) identical (m.p. and i.r. spectrum) to a sample prepared as described in (vii) (a) above. Further work-up as described in (vii) (a) yielded no identifiable material.

(viii) Heating the betaine (183) under reflux with aqueous sodium carbonate in ethanol (25 ml) for 2h gave 3-(5-oxopent-2-enylidene)amino-1-phenylcinnolin-4(1H)-one (184) which crystallised from the reaction mixture as yellow fibrous needles (48%), m.p. 210-212° (decomp.) (from benzene-dimethylformamide), $\nu_{max.}$ 3280m(NH), 1665m and 1620(CO) and 1600(C=C) cm^{-1}.

Found: C,71.8%; H,4.9%; N,13.1%; M^+317.
$C_{19}H_{15}N_3O_2$ requires: C,71.9%; H,4.8%; N,13.2%; M 317.

Evaporation of the aqueous ethanolic mother liquors, treatment with water (10 ml) and extraction with chloroform gave a deep red oil (0.91g) whose t.l.c. in chloroform over silica

showed it to be a multi-component mixture which was not further investigated.

17. The Attempted Cyclisation of the Hydrazone (206).

(i) In the Absence of p-Benzoquinone:- the hydrazone (206) (1.55g, 0.005 mol) in ethanol (250 ml) and water (30 ml) was heated under reflux with aqueous N sodium carbonate solution (12.5 ml). Evaporation of the mixture, treatment of the residue with water (50 ml) and extraction with chloroform gave a brown solid (1.35g) whose t.l.c. in chloroform-methanol over silica showed it to be a five component mixture. Dry-column chromatography in acetone over alumina failed to effect a separation of the mixture (recovery - 54%). Acidification of the aqueous layer and extraction with chloroform gave a small amount of red gum (0.10g) which was not further investigated.

(ii) In the Presence of p-Benzoquinone:- the hydrazone (206) (0.62g, 0.002 mol) and p-benzoquinone (0.22g, 0.002 mol) in ethanol (135 ml) were heated under reflux with aqueous N sodium carbonate solution (5.0 ml) for 3h. The solution became dark green and then black. Evaporation of the mixture, treatment with water (50 ml) and extraction with chloroform gave a dark red oil (0.44g). Acidification of the aqueous layer and extraction with chloroform gave a dark oil (0.20g). T.l.c. of both oils in chloroform or chloroform-methanol over silica showed them to be unresolvable multi-component mixtures which were not further investigated.

18. The Attempted Reaction of the Cinnolinone (182a) with Ethanolic Potassium Hydroxide.

The cinnolinone (182a) (0.27g, 0.001 mol) in ethanol (35 ml) was heated under reflux with 20% w/v aqueous potassium hydroxide solution

(2.5 ml) for 30 min. Evaporation of the dark solution and treatment of the residue with water (5.0 ml) gave a greenish brown solid (0.27g) which was shown by t.l.c. in chloroform over silica to be a multi-component mixture which could not be resolved on attempted recrystallisation from ethanol-light petroleum or benzene. Acidification of the aqueous mother liquors and extraction with chloroform yielded a negligible quantity of oily solid.

19. The Attempted Reaction of the Cinnolinone (182a) with Aqueous Sulphuric Acid in Glacial Acetic Acid.

The cinnolinone (182a) (0.27g, 0.001 mol) was heated under reflux with 20% w/v aqueous sulphuric acid (4.0 ml) in glacial acetic acid (10 ml) for 1h. Evaporation of the red solution and treatment with water (10 ml) produced starting material (96%), identical (m.p. and i.r. spectrum) with an authentic sample.

20. The Attempted Hydrogenation of the Cinnolinone (182a).

The cinnolinone (182a) (0.27g, 0.001 mol) in ethanol (40 ml) was hydrogenated at atmospheric pressure over 10% palladium-charcoal (0.06g). Little hydrogen uptake was observed and the mixture was filtered through Kieselguhr and evaporated to yield starting material (quantitative), identical (m.p. and i.r. spectrum) to an authentic sample.

21. The Reaction of the Cinnolinone (182a) with Aqueous Sodium Hypochlorite.

The cinnolinone (182a) (0.27g,0.001 mol) in dioxan (10 ml) and water (1.0 ml) was stirred at 70° for 1.5h with aqueous 3.85 N sodium hypochlorite solution. The excess of hypochlorite was

destroyed with sodium bisulphite solution and the mixture was diluted with water (20 ml) and extracted with chloroform to give the starting material (78%), identical (i.r. spectrum and m.p.) to an authentic sample. Acidification of the aqueous layer gave 1-phenylcinnolin-4(1H)-one-3-carboxylic acid (182d) (18%; 85% based on unrecovered starting material), m.p. 265-271° (lit.,[153] 275°), identical (m.p., mixed m.p. and i.r. spectrum) to a sample prepared as described in 16.(iii) above.

22. Oxidation of the Cinnolinone (182a) with Chromium Trioxide.

The cinnolinone (182a) (0.54g, 0.002 mol) and chromium trioxide (1.08g) in glacial acetic acid-water (7:3) (20 ml) were heated at 100° for 1h. The green solution was diluted with water (20 ml) and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium bicarbonate solution (20 ml) and evaporated to yield an unidentified intractable dark brown solid (0.31g). Acidification of the bicarbonate washings gave the carboxylic acid (182d) (26%), m.p. 266-271° (lit.,[153] 275°), identical (m.p. and i.r. spectrum) to an authentic sample prepared as described in 16.(iii) above.

23. The Attempted Methylation of the Cinnolinone (182a).

The cinnolinone (182a) (0.27g, 0.001 mol) in methanol (10 ml) was treated with methyl iodide (0.06 ml) and left at room temperature for 3 weeks. No solid was precipitated. Evaporation of the solution gave the starting material (quantitative), identical (m.p., t.l.c. in chloroform over silica and i.r. spectrum) to an authentic sample.

24. The Preparation and Cyclisation of 3-Acetyl-1-phenylcinnolin-4(1H)-one Hydrazone (192).

The cinnolinone (182a) (0.57g, 0.002 mol) and 100% hydrazine

hydrate (0.1 ml, 0.002 mol) in methanol (20 ml) were heated under reflux for 1.5h. Cooling the reaction mixture in ice gave 3-acetyl-1-phenylcinnolin-4(1H)-one hydrazone (192) as yellow needles (90%), m.p. 188-227° (decomp.) (from ethyl acetate-dimethylformamide), $\nu_{max.}$ 3375m and 3200m(NH_2), 1640(CO) and 1620(NH_2 deformation) cm^{-1}.

Found: C,68.6%; H,5.2%; N,19.7%; M^+278.

$C_{16}H_{14}N_4O$ requires: C,69.0%; H,5.1%; N,20.1%; M 278

The hydrazone (192) (0.28g, 0.001 mol) was heated under reflux in glacial acetic acid (5.0 ml) for 30 min. Evaporation of the solvent and crystallisation of the residue from ethyl acetate gave 3-methyl-5-phenylpyrazolo[4,3-c]cinnoline (193) as bright red needles (75%), m.p. 247-248° (decomp.) (from ethyl acetate).

Found: C,73.4%; H,4.5%; N,21.3; M^+260.

$C_{16}H_{12}N_4$ requires: C,73.8%; H,4.7%; N,21.5; M 260.

25. The Baeyer-Villiger Oxidation of the Cinnolinones (182a,b).

(i) The cinnolinone (182a) (0.27, 0.001 mol) in glacial acetic acid (5.0 ml) was heated at 50° for 15h with 30% aqueous hydrogen peroxide (2.5 ml). Careful concentration of the red solution and dilution with water (20 ml) gave 3-hydroxy-1-phenylcinnolin-4(1H)-one (182i) as pale yellow needles (92%), m.p. 226-227° (from ethanol), $\nu_{max.}$ 3200br(OH) and 1615(CO) cm^{-1}.

Found: C,70.4%; H,4.1%; N,12.0%, M^+238.

$C_{14}H_{10}N_2O_2$ requires: C,70.6%; H,4.2%; N,11.8%; M 238.

(ii) The cinnolinone (182b) (0.99g, 0.003 moles) in glacial acetic acid (35 ml) was heated at 50° for 68h with 30% aqueous hydrogen peroxide (7.5 ml). Dilution of the yellow solution with water (50 ml) gave 3-benzoyloxy-1-phenylcinnolin-4(1H)-one (182j) as colourless

prisms (66%), m.p. 164-165° (from ethanol), $\nu_{max.}$ 1740 and 1645(CO) cm^{-1}.

Found: C,73.8%; H,4.1%; N,8.4%; M^+342.

$C_{21}H_{14}N_2O_3$ requires: C,73.7%; H,4.1%; N,8.2%; M 342.

Extraction of the filtrate with chloroform and trituration of the resultant oil with toluene gave the hydroxy compound (182i) (21%), identical (m.p. and i.r. spectrum) to the sample prepared as described in (i) above. Evaporation of the trituration liquors and leaching with boiling light petroleum gave benzoic acid (27%), identical (m.p. and i.r. spectrum) with an authentic sample.

(iii) The benzoate (182j) (0.34g, 0.001 mol) in ethanol (10 ml) was heated under reflux for 30 min. with 10% w/v aqueous sodium hydroxide solution (2.5 ml). Evaporation of the mixture, treatment with water (2.5 ml) and acidification gave a brown solid (0.38g) which was leached with boiling light-petroleum to leave the insoluble hydroxy compound (182i) (92%), identical (m.p. and i.r. spectrum) to the sample prepared as described in (i) above. Evaporation of the light petroleum extract afforded benzoic acid (quantitative) identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample.

26. The Hydrolysis of the Cyanocinnolinone (182e).

The cyanocinnolinone (182e) (0.25g, 0.001 mol) in polyphosphoric acid (ca. 1.5 ml) was stirred at 80° for 3h. Treatment with water and rubbing produced a colourless solid which was crystallised from glacial acetic acid-water to give the amide (182f) as colourless prisms (80%), m.p. 285-289° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared as described in 16.(iv) (a) above.

27. The Attempted Degradation of the Cinnolinone (184).

(i) The cinnolinone (184) (0.32g, 0.001 mol) in ethanol (50 ml) was heated under reflux for 1h with dilute aqueous sulphuric acid (5.0 ml). The mixture became deep purple and finally lightened to yellow. Evaporation of the mixture, treatment with water (20 ml) and extraction with chloroform gave a deep red oil (0.05g). Basification of the aqueous layer with 10% w/v aqueous sodium hydroxide and extraction with chloroform gave a deep red oil (0.30g) smelling slightly of pyridine. Both red oils were shown by t.l.c. in chloroform or chloroform-methanol over silica to be multi-component mixtures from which no identifiable material could be obtained.

(ii) A solution of the cinnolinone (184) (0.32g, 0.001 mol) in glacial acetic acid (10 ml) was heated under reflux for 1h. Dilution with water (25 ml) and extraction with chloroform yielded a dark red oil (0.30 g) whose t.l.c. in chloroform over silica showed it to be a multi-component mixture from which no identifiable material could be obtained.

(iii) The cinnolinone (184) (0.32g, 0.001 mol) and aniline (0.10g, 0.001 mol) in ethanol (60 ml) were heated under reflux for 1h. The crimson solution was evaporated to give a dark red oil (0.45g) whose t.l.c. in chloroform or chloroform-methanol over silica showed it to be a multi-component mixture containing the starting material and aniline.

(iv) The cinnolinone (184) (0.32g, 0.001 mol) in dimethylformamide (50ml) was hydrogenated at room temperature and pressure over 10% palladium-charcoal. Filtration through Kieselguhr and dilution with water (100 ml) gave a dirty yellow solid (0.14g). Extraction of the filtrate with chloroform gave a deep red oil (0.16g). T.l.c. of both the solid and the oil in chloroform-

methanol over silica showed them to be unresolvable multi-component mixtures.

28. The Attempted Hydrolysis of the Cinnolinone (182h).

The nitrocinnolinone (182h) (0.27g, 0.001 mol) in acetic acid (10 ml) was heated under reflux for 12h with 20% w/v aqueous sulphuric acid (4.0 ml). The cooled red solution was poured into water (25 ml) to give the starting material as a pale brown solid (89%) identical (m.p. and i.r. spectrum) to an authentic sample.

29. The Attempted Reduction of the Nitrocinnolinone (182h) to the Amine (182k).

The nitrocinnolinone (182h) (1.08g, 0.004 mol) in ethanol (350 ml) was hydrogenated at room temperature and pressure over 10% palladium-charcoal. Three molar equivalents of hydrogen were absorbed. The mixture was filtered through Kieselguhr and evaporated to give a brown solid (A) (0.86g), $\nu_{max.}$ 3450w, 3350 and 3250(NH_2) and 1590(CO) cm^{-1}, M^+237. T.l.c. in chloroform-methanol over silica or ether or methanol over alumina showed this solid to be a two component mixture which did not contain the 3-hydroxycinnolinone (182i) and which could not be resolved by crystallisation from ethanol. Dry column chromatography in ether over alumina gave a small quantity of yellow solid (0.04g) m.p. 225-228° (decomp.) (from ethanol), $\nu_{max.}$ 3450 and 3350(NH_2), 1625(CO) and 1580(NH_2 deformation) cm^{-1}, M^+237, consistent with the expected amine (182k). The remainder of the material recovered from the column (total recovery 93%) was shown by t.l.c. to be an unresolvable three component mixture. Preparative t.l.c. in methanol-ether (1:9) over alumina

likewise failed to resolve the mixture.

The attempted acetylation of the original solid mixture (A) gave a red solid (quantitative) $\nu_{max.}$ 3300(NH) and 1700 and 1610(CO) cm^{-1}, which was shown by t.l.c. to be an unresolvable two component mixture.

30. The Reactions of the Active Methylene Compounds (180a,b) with Toluene-4-sulphonyl Azide.

Toluene-4-sulphonyl azide (96%) was prepared using the method described by Von Doering and De Puy[201] (96%), $\nu_{max.}$ 2150 ($N=N^{+}=N^{-}$) cm^{-1}.

(i) 2-Diazo-1-(2'-nitrophenyl)butane-1,3-dione (213b) was obtained as a yellow solid (56%), m.p. 93-98° (lit.,[175] 100°), by the piperidine-catalysed reaction of 2'-nitrobenzoylacetone (180a) with toluene-4-sulphonylazide as described by Regitz.[178]

(ii) 2-Diazo-1-(2'-nitrophenyl)-3-phenylpropane-1,3-dione (211) was obtained as a yellow solid (64%), m.p. 61-64° (lit.,[178] 67-70°) by the triethylamine-catalysed reaction of 2'-nitrodibenzoylmethane (180b) with toluene-4-sulphonyl azide as described by Regitz.[178]

31. The Preparation of 2-Hydrazono-1-(2'-nitrophenyl)-3-phenylpropane-1,3-dione (212).[178]

The hydrazone (212) was prepared as described by Regitz[178] by reacting the diazo compound (211) with triphenylphosphine to give the phosphazine (89%), m.p. 142-143° (decomp.) [lit.,[178] 139-140° (decomp.)] and subsequent acid hydrolysis to give the hydrazone (212) (87%), m.p. 157-158° (decomp.) [lit.,[178] 150° (decomp.)].

32. The Attempted Cyclisations of the Hydrazone (212).

The hydrazone (212) (0.30g, 0.001 mol) in ethanol (10 ml) was

heated under reflux for 30 min. with aqueous N sodium carbonate solution (2.5 ml). Evaporation of the red solution, treatment of the residue with water (10 ml) and extraction with chloroform gave a red oil (0.16g). Acidification of the aqueous layer and extraction with chloroform also gave a red oil (0.10g). T.l.c. in chloroform-methanol over silica showed both oils to be multi-component mixtures which could not be resolved.

Repetition of the reaction using aqueous N sodium acetate solution (2.5 ml) gave the same result.

33. The Attempted Reaction of the Hydrazone (212) with Toluene-4-sulphonyl Chloride in Pyridine.

A solution of the hydrazone (212) (0.75g, 0.0025 mol) in pyridine was stirred and treated at room temperature with toluene-4-sulphonyl chloride (0.45g, 0.0025 mol) and the mixture was stirred at room temperature for a further 22h. Evaporation of the red solution, treatment with dilute aqueous sulphuric acid (20 ml) and extraction with chloroform gave a red oil which on trituration with ether yielded the starting material (86%), identical (m.p. and i.r. spectrum) to an authentic sample.

34. The Reaction of the Diazo Compound (213b) with Potassium Cyanide.

The diazo compound (213b) (1.15g, 0.005 mol) in hot ethanol (10 ml) was treated with a solution of potassium cyanide (0.75g) in water (1.0 ml) and left at room temperature for 13h. The insoluble yellow salt (1.36g), $\nu_{max.}$ 2225m and 2175(C≡N), 1620(CO) and 1510 and 1360(NO_2) cm^{-1}, was collected, dissolved in water and acidified to give 2'-nitrophenylglyoxal 1-cyanohydrazone (214b) as a colourless solid (91%), m.p. 99-100° (decomp.), $\nu_{max.}$ 3300br(NH), 2250(C≡N),

1675(CO) and 1535 and 1355(NO_2) cm^{-1}, τ [$(CD_3)_2CO$] 1.76-1.89 (1H, m, ArH), 2.00-2.28 (2H, m, ArH), 2.33-2.48 (1H, m, ArH) and 2.22 (1H, s, H-1). The cyanohydrazone (214b) decomposed on attempted crystallisation.

Evaporation of the original mother liquors, treatment with water (10 ml), acidification and extraction with chloroform gave an orange intractable gum (0.20g) which was not investigated further.

35. The Attempted Cyclisation of the Cyanohydrazone (214b).

The cyanohydrazone (214b) (0.22g, 0.001 mol) in ethanol (5.0 ml) was heated under reflux for 26h with aqueous N sodium carbonate solution (2.5 ml). Evaporation of the red solution, treatment with water (10 ml), acidification and extraction with chloroform gave a pale brown solid (0.19g) whose t.l.c. in chloroform-methanol over silica showed it to be a mixture of the starting material and one other component. This solid decomposed on standing before it could be investigated further.

B. Benz-1,2-oxazinones

1. The Preparation of the Oximes (215 a-c).

The active methylene compounds (180 a,b and d)(0.015 mol) in glacial acetic acid were treated at room temperature with stirring over a period of 1 h with a solution of sodium nitrite (1.04 g, 0.015 mol) in water (4.0 ml). Stirring was continued at room temperature for a further 2 h and the mixture was then diluted with an equal volume of water and extracted with ether. Evaporation of the ether extract and removal of the acetic acid as the azeotrope with toluene gave the solid oximes which crystallised from benzene as mixtures of the syn and anti forms as indicated by their indistinct melting points.

(i) Nitrosation of 2'-nitrobenzoylacetone (180a) in glacial acetic acid (10 ml) gave 1-(2'-nitrophenyl)-2-oximinobutane-1,2,3-trione (215a) as buff-coloured prisms (80%), m.p. 87-111° (from benzene-light petroleum), $\nu_{max.}$ 3450 (OH), 1715 and 1670 (CO) and 1540 and 1350 (NO_2) cm^{-1}.

Found: C, 51.3%; H, 3.4%; N, 12.1%; M^+ 236.

$C_{10}H_8N_2O_5$ requires: C, 50.9%; H, 3.4%; N, 11.9%; M 236.

(ii) Nitrosation of 2'-nitrodibenzoylmethane (180b) in glacial acetic acid (100 ml) gave a product which was shown by t.l.c. in chloroform over silica to be a mixture of two components. Wet-column chromatography in light petroleum-toluene (9:1) over silica gave 1-(2'-nitrophenyl)-2-oximino-3-phenylpropane-1,2,3-trione (215b) as colourless prisms (64%), m.p. 145-154° (decomp.)(from benzene), $\nu_{max.}$ 3420 (OH), 1685 and 1665 (CO) and 1535 and 1355 (NO_2) cm^{-1}.

Found: C, 60.0%; H, 3.4%; N, 9.3%; M^+ 298.

$C_{15}H_{10}N_2O_5$ requires: C, 60.4%; H, 3.4%; N, 9.4%; M 298.

(iii) Nitrosation of 2'-nitrobenzoylacetonitrile (180d) in glacial acetic acid (40 ml) gave 2-oximino-2'-nitrobenzoylacetonitrile (215c) as colourless plates (87%), m.p. 135-143° (decomp.)(from benzene), $\nu_{max.}$ 3150 br (OH), 2290w (C≡N), 1695 (CO) and 1540 and 1350 (NO_2) cm^{-1}.

Found: C, 49.0%; H, 2.3%; N, 19.2%; M^+ 219.

$C_9H_5N_3O_4$ requires: C, 49.3%; H, 2.3%; N, 19.2%; M 219.

2. The Attempted Cyclisation of the Oxime (215a).

The oxime (215a) (3.54 g, 0.015 mol) in ethanol (100 ml) was heated under reflux with (a) aqueous N sodium carbonate solution (37.5 ml) or (b) aqueous N sodium acetate solution (37.5 ml) for 20 min. Evaporation of the red solution, treatment with water (40 ml) and extraction with chloroform gave a red oil (1.10 g) which on trituration with ether afforded 2'-nitrophenylglyoxylamide (222) as colourless needles (0.21 g, 7%), m.p. 192-194° (from ethanol) (lit.,[182] 199°), $\nu_{max.}$ 3475 and 3200 (NH_2) 1690 (CO) and 1540 and 1365 (NO_2) cm^{-1}, τ(CF_3CO_2H) 1.62-1.76 (1H, m, ArH) and 1.92-2.74 (5H, m, ArH and NH_2).

Found: C, 49.5%; H, 3.1%; N, 14.3%; M^+ 195.

$C_8H_6N_2O_4$ requires: C, 49.5%; H, 3.1%; N, 14.4%; M 194.

Evaporation of the trituration liquors gave a red oil which was subjected to wet-column chromatography over alumina. Elution with toluene-ether (9:1) gave almost pure ethyl 2-nitrobenzoate as a yellow oil (0.75 g, 25%), $\nu_{max.}$ 1725 (CO) and 1550 and 1370 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.03-2.22 (1H, m, ArH), 2.22-2.51 (3H, m, ArH), 5.62 (2H, q, J 7 Hz, $\underline{CH_2}$-CH_3) and 8.66 (3H, t, J 7 Hz, CH_2-$\underline{CH_3}$), identical (i.r. spectrum) to an authentic sample. Further elution gave ethyl salicylate (224) as a red oil (0.10g, 4%), $\nu_{max.}$ 3200 (OH) and 1675 (CO) cm^{-1}, τ($CDCl_3$) 2.15 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-6'), 2.46-3.26

(3H, m, ArH), 5.61 (2H, q, J 7 Hz, $\underline{CH_2}$-CH_3) and 8.60 (3H, t, J 7 Hz, CH_2-$\underline{CH_3}$), which gave a purple colour with iron (III) chloride in ethanol and was identical (i.r. spectrum) to an authentic sample. The oil was further identified as ethyl salicylate by reaction with benzoyl chloride in the presence of sodium hydroxide to give ethyl O-benzoylsalicylate (225) as a pale brown solid, m.p. 82-88° (lit.,[183] 86°). Elution with ether gave 2'-nitrophenylglyoxylamide (222) (0.17 g, 6%), m.p. 187-191°.

Acidification of the aqueous mother liquors gave 2-nitrobenzoic acid as a pale brown solid (0.75 g, 30%), identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample.

3. The Attempted Cyclisation of the Oxime (215b).

The oxime (215b) (0.90 g, 0.003 mol) in ethanol (30 ml) was heated under reflux for 30 min with aqueous N sodium carbonate solution (7.5 ml). Evaporation of the yellow solution, treatment with water (10 ml) and extraction with chloroform gave a pale yellow oil (0.29 g) which on trituration with ether gave 2'-nitrophenylglyoxylamide (222) (0.05 g, 8%), identical (m.p. and i.r. spectrum) to a sample obtained before. Evaporation of the ether filtrate gave a pale yellow oil (0.24 g) whose t.l.c. in chloroform over silica showed it to contain ethyl 2-nitrobenzoate, ethyl salicylate (224) and more 2-nitrophenylglyoxylamide (222). The mixture was not investigated further.

Acidification of the aqueous mother liquors and extraction with chloroform gave benzoic acid (0.26 g, 70%), identical (m.p. and i.r. spectrum) to an authentic sample.

The attempted cyclisation of the oxime (215a) using aqueous ethanolic sodium acetate as described before gave starting material (93%), identical (m.p. and i.r. spectrum) to an authentic sample.

4. The Cyclisation of the Oxime (215c).

(i) The oxime (215c) (0.66 g, 0.003 mol) in ethanol (10 ml) was heated under reflux for 16 h with aqueous N sodium acetate solution (7.5 ml). Evaporation of the solution and trituration of the residue with water (10 ml) gave 3-cyano-benz-1,2-oxazin-4-one (226) as colourless prisms (31%), m.p. 159-160° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1665 (CO) cm^{-1}.

Found: C, 62.4%; H, 2.3%; N, 16.1%; M^+ 172.

$C_9H_4N_2O_2$ requires: C, 62.8%; H, 2.3%; N, 16.3%; M 172.

Acidification of the aqueous mother liquors and extraction with chloroform gave a pale brown solid. This was extracted with boiling light petroleum to yield a colourless solid which was crystallised from benzene to give starting material (30%) identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) A solution of the oxime (215c) (4.4 g, 0.02 mol) in absolute ethanol (70 ml)was treated with a solution of sodium (0.46 g, 0.02 mol) in absolute ethanol (10 ml) and the mixture was stirred for 14 h at room temperature. Evaporation of the red solution, treatment with water (50 ml), acidification and extraction with chloroform gave the starting material (91%), identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) The oxime (215c) (0.44 g, 0.002 mol) in ethanol (10 ml) was heated under reflux with piperidine (0.20 ml) for 22 h. Evaporation of the red solution, treatment with water (10 ml) and extraction with chloroform gave a red oil which was triturated with ether to yield 3-cyanobenz-1,2-oxazin-4-one (226) (41%), identical (m.p., i.r. spectrum and t.l.c. in chloroform over silica) to a sample prepared as described in (i) above. The trituration liquors on evaporation gave a red oil (0.17 g) whose t.l.c. in ethyl acetate over alumina showed it to be a multi-component

mixture from which no identifiable material could be obtained. Acidification of the aqueous mother liquors and extraction with chloroform gave an oily solid which was crystallised from benzene to give the starting material (19%), identical (i.r. spectrum) to an authentic sample.

C. Miscellaneous Attempted Cyclisations involving Displacement of Aromatic Nitro Groups.

1. The Preparation of 2'-Nitrophenoxyacetone (228).[185]

2'-Nitrophenoxyacetone (228) was prepared as described by Stoermer and Brockerhof[185] (91%) and had m.p. 69-71° (lit.,[185] 69°).

2. The Attempted Reaction of 2'-Nitrophenoxyacetone (228) with Benzenediazonium Chloride.

(i) A solution of benzenediazonium chloride (0.0044 mol), prepared as described before, was added dropwise with stirring at 10-20° to a solution of 2'-nitrophenoxyacetone (228) (0.78 g, 0.004 mol) and sodium acetate (0.52 g) in ethanol (55 ml) and water (10 ml). The mixture was stirred at 10-20° for 1 h, evaporated, treated with water (20 ml) and extracted with chloroform to give an oily solid which on crystallisation from aqueous methanol gave the starting material (77%), identical (i.r. spectrum to an authentic sample.

(ii) A solution of benzenediazonium chloride (0.0044 mol), prepared as described before, was added dropwise with stirring at 0° to a solution of 2'-nitrophenoxyacetone (228) (0.78 g, 0.004 mol) in absolute ethanol (50 ml) which had been treated with a solution of sodium (0.15 g) in absolute ethanol (5.0 ml). The mixture was stirred at 0° for 1 h, evaporated, treated with water (20 ml) and extracted with chloroform to give a deep red oil (0.83 g) whose t.l.c. in chloroform-ether over silica showed it to be a multi-component mixture from which no identifiable material could be obtained.

3. The Attempted Reaction of the N,N-Disubstituted Benzamide (231)[186] with Benzenediazonium Chloride.

A solution of benzenediazonium chloride (0.0044 mol), prepared as described before, was added dropwise with stirring at 10-20° to a solution of N-cyanomethyl-N-phenyl-2-chloro-5-nitrobenzamide (231)[186] (1.26 g, 0.004 mol) and sodium acetate (0.52 g) in acetone (100 ml) and water (16 ml). The mixture was stirred at 10-20° for 1 h, evaporated, treated with water (20 ml) and extracted with chloroform to give the starting material (95%), identical to an authentic sample.

4. The Reaction of the Diketone (180a) with Phenyl Isothiocyanate.

(i) A solution of 2'-nitrobenzoylacetone (180a) (1.04 g, 0.005 mol) and phenylisothiocyanate (0.70 g, 0.0055 mol) in absolute ether (15 ml) was left at room temperature for 4 days or heated under reflux for 16 h. T.l.c. of the mixture in chloroform over silica showed only the presence of the starting diketone (180a) and phenylisothiocyanate. Performing the reaction in refluxing toluene (16 h) produced the same result.

(ii) A solution of the diketone (180a) (1.04 g, 0.005 mol) in absolute ethanol (15 ml) was treated with a solution of sodium (0.23 g, 0.005 mol) in absolute ethanol (2.5 ml), stirred at room temperature for 30 min. and evaporated to give a gummy yellow sodium salt which was dissolved in dimethylformamide (25 ml) and treated with phenylisothiocyanate (0.70 g, 0.0055 mol). The mixture was left at room temperature for 7 days and was then diluted with water (50 ml) and extracted with chloroform to give an oily residue which was pumped down under high vacuum (to remove dimethylformamide) giving a dark red oil (0.80 g). T.l.c. in ether-benzene over silica showed this to be a multi-component mixture from which no identifiable material could be obtained.

Acidification of the aqueous mother liquors and extraction with chloroform gave a dark red oil which on standing for 2 weeks partially solidified. Trituration with chloroform gave a yellow solid (0.32 g) which on crystallisation from ethanol gave 2'-nitrobenzoyl-N-phenyl-thioacetamide (239) as yellow plates (0.24 g, 16%), m.p. 142-143°, $\nu_{max.}$ 3220 m (NH), 1635 (CO) and 1540 and 1365 (NO_2) cm^{-1}.

Found: C, 60.1%; H, 4.0%; N, 9.1%; M^+ 300.

$C_{15}H_{12}N_2O_3S$ requires: C, 60.0%; H, 4.0%; N, 9.3%: M 300.

Evaporation of the trituration liquors gave a red oil (0.83 g) whose t.l.c. in ether-benzene over silica showed it to be a multi-component mixture from which no identifiable material could be obtained.

5. The Preparation of 2'-Nitrobenzoylazide (240b).

2'-Nitrobenzoylazide (240b) was prepared as described by Naegeli, Tyabji and Conrad[188] (98%) and had m.p. 37-39° (lit.,[188] 40-41°).

6. The Reaction of 2'-Nitrobenzoylazide (240b) with Phenylmagnesium Bromide.

A solution of phenylmagnesium bromide in ether prepared by the reaction under nitrogen of magnesium turnings (0.01 mol) and bromobenzene (0.01 mol) in sodium-dried ether (10 ml) was cooled to -70° in an alcohol-dry ice bath under a stream of dry nitrogen. The azide (240b) (1.92 g, 0.01 mol) in sodium-dried ether (20 ml) was added dropwise with stirring over a period of 1 h. Stirring was continued for a further 3 h and the red solution was warmed to -20° and treated with ethanol (2 ml) to decompose any unreacted Grignard reagent. The mixture was then allowed to warm to 0° and was poured into an ice-cold solution of ammonium chloride (4.5 g) in water (12.5 ml). Extraction with chloroform gave a dark gummy solid

(1.97 g) which was triturated with methanol to give 2'-nitrophenylurea (245) as yellow needles (0.17 g, 9%), m.p. 177-178° (lit.,[189] 181°), $\nu_{max.}$ 3450, 3320 and 3200 (NH), 1670 (CO) and 1520 and 1350 (NO_2)cm^{-1}.

Found: C, 46.7%; H, 3.9%; N, 23.2%; M^+ 181.

$C_7H_7N_3O_3$ requires: C, 46.4%; H, 3.9%; N, 23.2%; M 181.

Evaporation of the trituration liquors gave a dark red intractable gum (1.80 g) whose t.l.c. in ether-benzene over silica showed it to be a multi-component mixture. Acidification of the aqueous mother liquors and extraction with chloroform gave a dark intractable gum (0.15 g) which was not further investigated.

PART II

Miscellaneous Attempted Cyclisations Involving Other Types of Nitro Group Participation

1. The Preparation of 3'-Methoxy-2-nitrobenzhydrol (251).

A solution of 2-nitrobenzaldehyde (9.6 g, 0.064 mol) in sodium-dried toluene (140 ml) was cooled to -70° and treated dropwise under nitrogen with stirring over a period of 1.5 h with a solution of 3-methoxyphenylmagnesium bromide in absolute ether [prepared by the reaction of magnesium turnings (1.72 g, 0.072 mol) and 3-bromoanisole (13.2 g, 0.072 mol) in sodium-dried ether (25 ml)]. Stirring was continued for 2 h at -70° and the pale brown solution was allowed to warm to -20° when ethanol (10 ml) was added to decompose any unreacted Grignard reagent. After further warming to 0°, the solution was poured into an ice-cold solution of ammonium chloride (12.0 g) in water (240 ml) and left at 0° overnight. The organic layer was shaken with saturated aqueous sodium bisulphite solution to give the bisulphite addition complex of 2-nitrobenzaldehyde (1.02 g), identical (i.r. spectrum) to an authentic sample. The organic layer was washed with water, dried and evaporated to yield a yellow oil which on trituration with ether gave 3'-methoxy-2-nitrobenzhydrol (251) as a colourless amorphous solid (9.75g, 59%), m.p. 69-70° (from benzene-light petroleum), $\nu_{max.}$ 3500 (OH) and 1525 and 1340 (NO_2) cm^{-1}, $\tau(CDCl_3)$ 2.12 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-3), 2.25-2.88 (4H, m, ArH), 3.07-3.29 (3H, m, ArH), 3.65 (1H, s, CH), 6.28 (3H, s, OMe) and 6.80-7.60 (1H, br, OH).

Found: C, 65.2%; H, 5.0%; N, 5.4%; M^+ 259.

$C_{14}H_{13}NO_4$ requires: C, 64.9%; H, 5.1%; N, 5.4%; M 259.

The trituration liquors on evaporation gave a brown oil (5.50 g) whose t.l.c. in chloroform over silica showed it to be an unresolvable five component mixture containing more product.

2. The Attempted Reaction of the Benzhydrol (251) with Toluene-4-sulphonyl Chloride.

The benzhydrol (251) (1.30 g, 0.005 mol) in pyridine (5.0 ml) was stirred with toluene-4-sulphonyl chloride (0.95 g, 0.005 mol) at room temperature for 24 h. The red solution was dissolved in chloroform and washed with dilute aqueous sulphuric acid (2 x 10 ml) and water (10 ml). Evaporation of the organic layer gave a red oil (1.20 g) which was shown by t.l.c. in chloroform-benzene over silica to be a three component mixture consisting mainly of starting material.

3. The Attempted Reaction of the Benzhydrol (251) with Polyphosphoric Acid.

The benzhydrol (251) (1.00 g, 0.004 mol) was stirred in polyphosphoric acid (12.6 g, ca. 6 ml) at 50° for 3 h. The dark green solution was treated with ice (20 g) and scratched to produce a dark brown intractable solid (0.90 g) whose t.l.c. in chloroform over silica showed it to be an unresolvable multi-component mixture. Extraction of the filtrate with chloroform gave an intractable red gum (0.10 g).

4. The Attempted Reaction of the Benzhydrol (251) with Boron Trifluoride.

The benzhydrol (251) (0.52 g, 0.002 mol) in sodium-dried ether (20 ml) was treated with boron trifluoride etherate (5.0 ml), heated under reflux for 15 min and poured into water (25 ml). Evaporation of the organic layer gave a dark green intractable gum (0.60 g) from which no identifiable material could be obtained.

5. The Attempted Reaction of the Benzhydrol (251) with 98% Formic Acid.

The benzhydrol (251) (0.52 g, 0.002 mol) in 98% formic acid (3.0 ml) was left at room temperature for 36 h. The dark solution was poured into water (15 ml) and extracted with chloroform which, after washing

with 10% w/v aqueous sodium hydroxide (2 x 10 ml) and water (10 ml), was evaporated to give a dark brown oil (0.50 g). Trituration of the oil with ether gave an unidentified pale brown solid (0.08 g), m.p. 100-111° (decomp.), $\nu_{max.}$ 1675 (CO) cm^{-1}, $\tau(CDCl_3$-60 MHz) 2.15-2.95 (8H, m, ArH) and 6.15 (3H, s, OMe), M^+ 241, which gave a green solution when dissolved in chloroform. Evaporation of the trituration liquors gave a red oil (0.42 g) which was shown by t.l.c. in chloroform over silica to be an unresolvable six component mixture.

6. The Preparation of Ethyl 2-Nitrophenylcarbonate (255).

Ethyl 2-nitrophenylcarbonate (255) (18.25 g, 87%) was prepared by the reaction of 2-nitrophenol (13.9 g, 0.1 mol) and ethyl chloroformate (14.1 g, 0.13 mol) using the method of Smith etal.[192] and had b.p. 106-113°/0.05 mm (lit.,[192] 116-118°/0.5 mm).

7. The Attempted Catalytic Hydrogenation of Ethyl 2-Nitrophenylcarbonate (255).

Ethyl 2-nitrophenylcarbonate (255) (0.84 g, 0.004 mol) in ethanol (50 ml) was hydrogenated at room temperature and pressure over 10% palladium-charcoal (0.05 g). Filtration through Kieselguhr and evaporation of the filtrate gave a red oil which solidified on rubbing (0.71 g) and was shown by t.l.c. in chloroform over silica to be a mixture of two components with a trace of a third. Crystallisation from benzene-light petroleum failed to resolve the mixture. The mixture, which was entirely soluble in 10% w/v aqueous sodium hydroxide, gave a deep red colour in the presence of iron (III) chloride. Attempted dry-column chromatography of the mixture in methanol over alumina resulted in the loss of 79% of the material on the alumina. The material recovered was a red intractable gummy solid (0.15 g).

8. The Attempted Sodium Borohydride-Palladium-charcoal Reduction of Ethyl 2-Nitrophenylcarbonate (255).

Ethyl 2-nitrophenylcarbonate (255) (2.11 g, 0.01 mol) in methanol (20 ml) was added under nitrogen over a period of 5 min to a stirred suspension of 10% palladium-charcoal (0.05 g) in water (20 ml) containing sodium borohydride (0.76 g, 0.02 mol). Stirring was continued for a further 15 min. Filtration through Keiselguhr and extraction with chloroform gave a red oil (1.21 g) which was shown by t.l.c. in chloroform over silica to be a multi-component mixture which was mainly starting material. Neutralisation of the aqueous layer and extraction with chloroform gave 2-aminophenol (0.30 g, 27%), m.p. 166-170° (lit.,[193] 176°), M^+ 109, (M 109). Acetylation with acetic anhydride gave 2-acetylaminophenol, m.p. 200-204° (lit.,[193] 209°), τ($CDCl_3$) 0.56 (1H, br, OH or NH), 0.86 (1H, br, OH or NH), 2.91-3.32 (4H, m, ArH) and 7.83 (3H, s, Me), M^+ 151 (M 151).

9. The Preparation of 2-Nitrothiocyanatobenzene (256).

2-Nitrothiocyanatobenzene (256) (7.60, 68%), m.p. 128-130° (from ethanol) (lit.,[195] 136°), was prepared by the treatment of 2-nitrobenzenediazonium chloride (0.062 mol) with potassium thiocyanate (17.4 g, 0.18 mol) in the presence of cobaltous chloride (15.0 g, 0.063 mol) using the method of Wagner-Jauregg and Helmert.[195]

10. The Attempted Catalytic Hydrogenation of 2-Nitrothiocyanatobenzene (256).

(i) 2-Nitrothiocyanatobenzene (256) (0.54 g, 0.003 mol) in ethanol (75 ml) or glacial acetic acid (35 ml) was hydrogenated at room temperature and pressure over 10% palladium-charcoal (0.05 g). There was no uptake of hydrogen and filtration through Kieselguhr and evaporation of the filtrate gave the starting-material (0.48 g, 90%), identical (i.r. spectrum) to an authentic sample.

(ii) 2-Nitrothiocyanatobenzene (256) (1.10 g, 0.006 mol) in ethanol (150 ml) was hydrogenated over Raney nickel (type W4) catalyst (0.3 g) under a pressure of three atmospheres for a period of 20 h. Filtration to remove the catalyst and evaporation gave a yellow solid which was washed with 10% w/v aqueous sodium hydroxide to give starting material (0.87 g, 80%), identical (i.r. spectrum and t.l.c. in chloroform-methanol over silica) to an authentic sample. Neutralisation of the basic washings by treatment with dilute aqueous hydrochloric acid followed by sodium acetate gave 2-aminobenzthiazole 3-oxide (257) (0.10 g, 10%; 50% based on unrecovered starting material), m.p. 165-180° (decomp.) [lit.,[194] 185-186° (decomp.)], $\nu_{max.}$ 3350 and 3250 (NH_2) and 1625 (NH deformation) cm^{-1}, which gave a deep blue-green colour in the presence of iron (III) chloride. Acetylation with acetic anhydride gave 2-acetylaminobenzthiazole 3-oxide, m.p. 187-193° (decomp.)[lit.,[194] 195-197° (decomp.)], $\nu_{max.}$ 2800-2400 (NH) and 1685 (CO) cm^{-1}, τ(CF_3CO_2H; 60 MHz) 1.85-2.40 (4H, m, ArH) and 7.33 (3H, s, Me).

The reaction on being repeated under a pressure of five atmospheres gave starting material (0.60 g, 55%), identical (i.r. spectrum and t.l.c. in chloroform-methanol over silica) to an authentic sample, and 2-aminobenzthiazole 3-oxide (257) (0.17 g, 17%; 38% based on unrecovered starting material), identical (i.r. spectrum) to the sample prepared as described before.

(iii) 2-Nitrothiocyanatobenzene (256) (0.72 g, 0.004 mol) in ethanol (150 ml) was hydrogenated over Raney nickel (type W6) catalyst (0.3 g) under a pressure of three atmospheres for 5 h. Filtration to remove the catalyst and evaporation of the filtrate gave a yellow solid which was washed with 10% w/v aqueous sodium hydroxide solution to yield starting material (0.48 g, 67%), identical (i.r. spectrum and t.l.c. in

chloroform-methanol over silica) to an authentic sample. Neutralisation of the basic washings by treatment with dilute aqueous hydrochloric acid followed by sodium acetate and extraction with chloroform gave a yellow intractable gum (0.07 g).

11. The Attempted Reduction of 2-Nitrothiocyanatobenzene (256) with Ammonium Sulphide.

Hydrogen sulphide was passed, with stirring over a period of 2 h, into a solution of 2-nitrothiocyanatobenzene (256) (2.70 g, 0.015 mol) in ethanol (270 ml) which had previously been treated with ethanol (15 ml) saturated with ammonia. Stirring was continued for 24 h and the black solution was concentrated to ca. 80 ml to give a yellow solid (2.41 g) which was shown (i.r. spectrum) to be mainly sulphur containing some starting material. The yellow filtrate was evaporated to give an oily yellow solid. Trituration with ether gave a pale brown solid which on crystallisation from aqueous ethanol yielded starting material (0.52 g, 20%), identical (i.r. spectrum) to an authentic sample. Evaporation of the trituration liquors gave a brown intractable oil (1.00 g) from which no identifiable material could be obtained.

12. The Reduction of 2-Nitrothiocyanatobenzene (256) with Zinc and Ammonium Chloride.

Zinc dust (0.60 g, 0.0095 g atom) was added over a period of 20 min to a well-stirred solution of 2-nitrothiocyanatobenzene (256) (1.10 g, 0.006 mol) and ammonium chloride (0.60 g, 0.011 mol) in dioxan-water (3:2) (70 ml). After stirring for a further 15 min., the mixture was diluted with water (45 ml), filtered and the residue washed with chloroform.

Extraction of the filtrate with chloroform and evaporation of the combined chloroform extracts gave an oily solid which on trituration with a little ether gave starting material (0.40 g, 37%), identical (i.r. spectrum and t.l.c. in chloroform-methanol over silica) to an authentic sample. Evaporation of the trituration liquors gave a dark green intractable oil (0.65 g) which was shown by t.l.c. in chloroform-methanol to be a multi-component mixture containing starting material.

13. The Preparation of 2'-Nitrophenylthioacetonitrile (260).

A solution of sodium hydroxide (1.6 g, 0.04 mol) in water (3.0 ml) was added dropwise to a stirred suspension of di-(2-nitrophenyl)disulphide (3.0 g, 0.01 mol) and D-glucose (2.1 g, 0.012 mol) in ethanol (10 ml) with gentle warming. Stirring and warming were continued until a solution was obtained (ca. 0.75 h). After cooling to room temperature, chloroaceto-nitrile (0.76 g, 0.01 mol) was added and the mixture was warmed for 5 min, cooled, treated with more chloroacetonitrile (0.76 g, 0.01 mol) and warmed for 10 min. Cooling the mixture in ice gave a yellow gummy solid which after washing with water was crystallised from ethanol to give 2'-nitrophenylthioacetonitrile (260) as yellow needles (2.35 g, 60%), m.p. 108-113° (lit.,[197] 117°).

14. The Attempted Cyclisations of 2'-Nitrophenylthioacetonitrile (260).

(i) The nitro compound (260) (0.40 g, 0.002 mol) in ethanol (30 ml) was treated with triethylamine (0.30 ml, 0.0022 mol) and the solution was heated under reflux for 1 h. Evaporation of the cooled solution gave starting material (0.37 g, 93%), identical (i.r. spectrum) to an authentic sample.

(ii) The nitro compound (260) (0.40 g, 0.002 mol) in ethanol (10 ml) was heated under reflux with aqueous N sodium acetate solution (5.0 ml) for 2 h. Evaporation of the solution and treatment with water (5.0 ml) gave starting material (0.37 g, 93%), identical (i.r. spectrum) to an authentic sample.

(iii) The nitro compound (260) (0.40 g, 0.002 mol) in ethanol (10 ml) was heated under reflux with aqueous N sodium carbonate solution (5.0 ml) for 1 h. Evaporation of the dark red solution, treatment with water (10 ml) and extraction with chloroform gave a dark red intractable gum (0.29 g) which was shown by t.l.c. in chloroform or chloroform-methanol over silica to be a multi-component mixture. Acidification of the aqueous layer and extraction with chloroform gave a red intractable gum (0.10 g) which was shown by t.l.c. to be a multi-component mixture.

(iv) The nitro compound (260) (0.40 g, 0.002 mol) in ethanol (50 ml) was stirred at room temperature with aqueous N sodium carbonate solution (5.0 ml) for 20 h. Evaporation of the solution and treatment with water (10 ml) and a little ether gave starting material (0.20 g, 50%), identical (i.r. spectrum and t.l.c. in chloroform over silica) to an authentic sample. The ether extract on evaporation gave an orange oil (0.12 g) which was shown by t.l.c. in chloroform over silica to be a multi-component mixture. Neutralisation of the aqueous layer with dilute aqueous hydrochloric acid followed by sodium acetate and extraction with chloroform gave a yellow intractable solid (0.02 g).

(v) The nitro compound (260) (0.40 g, 0.002 mol) in absolute ethanol (50 ml) was treated with stirring at room temperature with a solution of sodium (0.19 g, 0.008 mol) in absolute ethanol (5.0 ml). The dark red solution was stirred for 1 h, evaporated, treated with water (10 ml) and extracted with chloroform to give a dark red intractable

oil (0.12 g) which was shown by t.l.c. in chloroform over silica to be a multi-component mixture containing no starting material. Acidification of the aqueous layer and extraction with chloroform gave a red oil which on trituration with chloroform gave di-(2-nitrophenyl)disulphide (0.03 g), identical (i.r. spectrum and t.l.c. in chloroform over silica) to an authentic sample. Evaporation of the trituration liquors gave a dark red oil (0.24 g) which was shown by t.l.c. in chloroform over silica to be a multi-component mixture containing di-(2-nitrophenyl)disulphide.

15. The Preparation of N-Methyl-N-(2-nitrobenzyl)aminoacetonitrile (263).

A solution of 2-nitrobenzylchloride in ethyl methyl ketone (5.0 ml) was added dropwise with stirring at 0-10° to a mixture of N-methylamino-acetonitrile hydrochloride (3.15 g, 0.03 mol) and sodium bicarbonate (5.89 g, 0.07 mol) in ethyl methyl ketone (30 ml). The resultant mixture was heated under reflux for 6 h. Hot filtration to remove the inorganic solid and evaporation of the filtrate gave an orange oil (4.82 g) whose t.l.c. in benzene over silica showed it to be a three component mixture which was separated by column chromatography over alumina. Elution with light petroleum gave unreacted 2-nitrobenzyl chloride (0.52 g, 15%), identical (i.r. spectrum and t.l.c.) to an authentic sample. Elution with 50% toluene-light petroleum gave an orange oil (3.30 g), $\tau(CCl_4)$ 2.17-2.32 (m, ArH), 2.45-2.73 (m, ArH), 2.84-3.01 (m, ArH), 6.16 (s, CH_2), 6.65 (s, CH_2) and 7.74 (s, NMe), M^+ 204 (M 205), which was dissolved in ether and saturated with hydrogen chloride to give the crude hydrochloride (3.1 g). Crystallisation from ethanol gave N-methyl-N-(2'-nitrobenzyl)aminoacetonitrile hydrochloride (265) as a colourless amorphous solid (2.6 g, 54%; 63% based on unrecovered 2-nitrobenzylchloride), m.p. 127-128°, $\nu_{max.}$ 2600-2100 (N^+H) and 1540

and 1350 (NO_2)cm^{-1}, τ (CF_3CO_2H) 1.51-1.64 (1H, m, ArH), 1.98-2.24 (3H, m, ArH), 4.98 (1H, br, CH), 5.04 (1H, br, CH), 5.25 (2H, s, CH_2CN) and 5.50 (3H, s, NMe).

Found: C, 50.0%; H, 5.1%; N, 17.3%; M^+ 204.

$C_{10}H_{12}N_3O_2Cl$ requires: C, 49.7%; H, 5.0%; N, 17.4%; M 205.

The filtrate from the formation of the hydrochloride gave, on evaporation, a dark brown intractable oil (0.63 g).

Elution of the column with ether gave an unidentified red oil (0.33 g).

16. The Attempted Cyclisation of the Nitro Compound (263).

i) The amine hydrochloride (265) (0.48 g, 0.002 mol) in ethanol (25 ml) was heated under reflux with aqueous N sodium carbonate solution (5.0 ml) for 1 h. Evaporation of the yellow solution, treatment with water and extraction with ether gave N-methyl-N-(2'-nitrobenzyl)amino-acetonitrile (263) as a brown crystalline solid (0.35 g, 86%), m.p. 35-37°, $\nu_{max.}$ 1530 and 1365 (NO_2) cm^{-1}, τ($CDCl_3$) 2.06-2.20 (1H, m, ArH) 2.30-2.63 (3H, m, ArH), 6.06 (2H, s, CH_2), 6.55 (2H, s, CH_2) and 7.65 (3H, s, NMe), M^+ 204 (M 205), which could not be crystallised for further characterisation.

ii) A solution of sodium (0.19 g, 0.008 mol) in absolute ethanol (6.0 ml) was added dropwise with stirring at room temperature to a suspension of the amine hydrochloride (265) (0.48 g, 0.002 mol) in absolute ethanol (15 ml) and the mixture was stirred at room temperature for 3 h. The dark red solution was evaporated, treated with water (10 ml) (A) and extracted with chloroform which, after washing with dilute aqueous hydrochloric acid (15 ml) (B) and evaporation, gave a dark red intractable oil (0.09 g), $\nu_{max.}$ 1680 (CO) and 1540 and 1365 (NO_2) cm^{-1}. Acidification of the basic aqueous layer (A) and extraction

with chloroform gave a dark red intractable oil (0.05 g). Basification of the acidic aqueous layer (B) with solid sodium bicarbonate and extraction with chloroform gave a red oil (0.31 g), $\nu_{max.}$ 1680 (CO), 1630 and 1540 and 1365 (NO_2) cm^{-1}, which on dissolving in ether and saturating with hydrogen chloride gave no solid material.

18. The Preparation of N-Cyanomethyl-N-methyl-2-nitrophenylsulphenamide (266).

N-Methylaminoacetonitrile hydrochloride (1.06 g, 0.01 mol) was added in portions over a period of 2 h at room temperature to a well stirred suspension of sodium bicarbonate (1.80 g) and 2-nitrophenylsulphenyl chloride (1.89 g, 0.01 mol) in dry acetone (50 ml). Stirring was continued for 1.5 h and the inorganic material was removed by filtration. Evaporation of the filtrate gave a yellow oily solid (1.86 g) which was shown by t.l.c. in chloroform over silica to be mainly a two component mixture. This was separated by column chromatography over alumina. Elution with 50% toluene-light petroleum gave unreacted 2-nitrophenylsulphenyl chloride (0.26 g, 14%), identical (i.r. spectrum and t.l.c. in chloroform over silica) to an authentic sample. Elution with toluene gave N-cyanomethyl-N-methyl-2'-nitrophenylsulphenamide (266) as yellow prisms (1.00 g, 45%), m.p. 92-92.5° (from benzene-light petroleum), $\nu_{max.}$ 1520 and 1345 (NO_2) cm^{-1}, $\tau(CDCl_3)$ 1.70 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-3'), 2.14 (1H, dt, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5'), 2.33 (1H, dd, J_{ortho} 7 Hz, J_{meta} 2 Hz, H-6'), 2.58-2.77 (1H, m, H-4'), 6.03 (2H, s, CH_2) and 6.95 (3H, s, NMe).

Found: C, 48.5%; H, 4.1%; N, 18.8%; S, 14.3%; M^+ 223.

$C_9H_9N_3O_2S$ requires: C, 48.4%; H, 4.0%; N, 18.8%; S, 14.3%; M 223.

Elution with ether-toluene (1:3) gave an unidentified yellow solid (0.26 g, 12%), m.p. 185-186° (from ethanol-glacial acetic acid), $\nu_{max.}$ 1525 and 1345 (NO_2) cm^{-1}, $\tau(CDCl_3)$ 1.70-1.87 (m, ArH), 2.30-2.83 (m, ArH), 5.76 (s, CH), 6.89 (s, CH) and 7.53 (s, CH).

Found: C, 51.7%; H, 3.8%; N, 13.5%; M^+ 416.

$C_{18}H_{16}N_4O_4S_2$ requires: C, 51.9%; H, 3.9%; N, 13.5%; M 416.

19. The Attempted Cyclisation of the Nitro Compound (266).

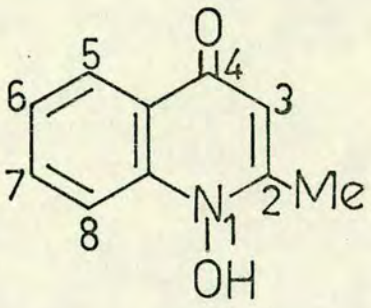
A solution of sodium (0.19 g, 0.008 mol) in absolute ethanol (10 ml) was added to a solution of the sulphenamide (266) (0.45 g, 0.002 mol) in absolute ethanol (15 ml) and the mixture was heated under reflux for 5 min. The dark red solution was evaporated, treated with water (25 ml) and extracted with chloroform to give an intractable brown gum (0.17 g). Acidification of the aqueous layer and extraction with chloroform gave a brown gum which on trituration with benzene-light petroleum gave a pale brown unidentified solid (0.07 g), m.p. 115-117°, $\nu_{max.}$ 1525 and 1340 (NO_2) cm^{-1}, $\tau(CDCl_3)$ 1.92 (dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, ArH), 2.17 (dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, ArH), 2.32-2.76 (m, ArH), 3.51 (s, CH), 6.12 (q, J 7 Hz, $\underline{CH_2}$-CH_3) and 8.81 (t, J 7 Hz, CH_2-$\underline{CH_3}$). Evaporation of the trituration liquors and trituration with light petroleum gave an unidentified pale brown solid (0.07 g), $\nu_{max.}$ 1660 (CO) and 1525 and 1345 (NO_2) cm^{-1}.

CHAPTER FOUR

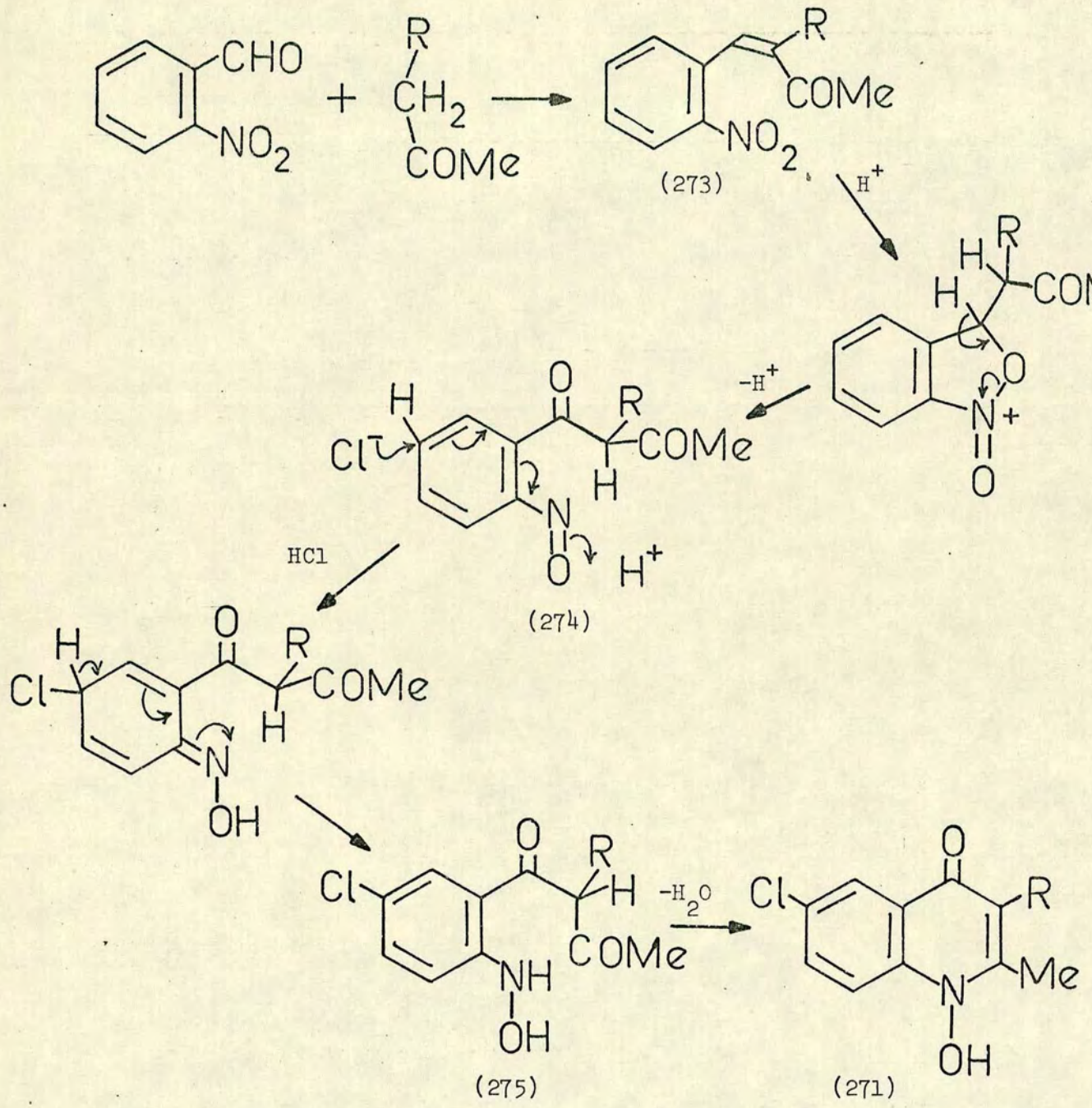
DISCUSSION

Nucleophilic Substitution Reactions of N-Oxygenated Heterocycles Derived from Ortho-Nitrobenzene Derivatives

Part 1. 1-Hydroxy-2-methylquinolin-4(1H)-ones



The mechanisms of the reactions of 2-methylpyridine 1-oxide (126)[107] and 2-methylquinoline 1-oxide (268)[108] with acetic anhydride have been thoroughly investigated (cf. Chapter 1). It is believed that the intermediate involved is an anhydro base of the type (269) which undergoes rearrangement to give the product, an acetoxymethyl derivative (270). 1-Acetoxy-2-methylquinolin-4-ones (272) which are readily available by acetylation of the corresponding N-hydroxyquinolinones (271)[202] bear certain structural similarities to the anhydro base (cf. 269), the proposed intermediate in the reaction of 2-methylquinoline 1-oxide (268) with acetic anhydride. Thus, it was thought that the investigation of the reactions of N-hydroxyquinolinones (271) and their N-acetoxy derivatives (272) with acylating agents might be a profitable area of study. With this aim in mind, the known N-hydroxyquinolinones (271a and b) were prepared by the hydrogen chloride-catalysed condensation[202] of 2-nitrobenzaldehyde with acetylacetone and ethyl acetoacetate, respectively. The mechanism of these condensations (Scheme 20) is believed to involve the initial formation of the benzylidene compound (273), followed by intramolecular oxygen transfer to give the intermediate nitroso compound (274). Reduction of (274) to the hydroxylamine (275), which undergoes cyclisation to the final product (271) by condensation of the hydroxylamino group


CHO
NO2
R
CH2
COMe
COMe
NO2
(273)
H+
R
H
H
COMe
O
N+
O
-H+
H
Cl
O
R
COMe
H
N
O
H+
(274)
HCl
H
Cl
O
R
COMe
H
N
OH
Cl
O
R
H
COMe
NH
OH
(275)
-H2O
Cl
O
R
Me
N
OH
(271)

Scheme 20

with the ortho-side chain, is accomplished by attack of chloride ion at the position para to the nitroso group. Also isolated in the reaction of 2-nitrobenzaldehyde with acetylacetone was a moderate yield of the intermediate benzylidene compound (273a). Similarly, in the analogous reaction of ethyl acetoacetate, a brown oil was obtained whose ^{1}H n.m.r. spectrum showed it to be a 2:1 mixture of the geometric isomers (273b and c) of the intermediate benzylidene compound. The products (271a and b) of these cyclisations are formulated as N-hydroxyquinolinones on the basis of their i.r. spectra. They both showed a broad hydroxyl band at 2300-2800 cm^{-1} and produced deep red colours in the presence of iron (III) chloride, properties characteristic[202] of N-hydroxy compounds. In addition, (271a) formed an N-acetoxy derivative (272a)[202] on mild treatment with acetic anhydride which showed carbonyl absorption at 1795 cm^{-1} in its i.r. spectrum, characteristic[202] of an N-acetoxy group.

In an effort to extend the scope of the N-hydroxyquinolinone synthesis, attempts were made to condense 2-nitrobenzaldehyde with a variety of other active methylene compounds. It had been reported[203] previously that the hydrogen chloride-catalysed reaction of benzoylacetone with 2-nitrobenzaldehyde afforded the N-hydroxy-3-benzoylquinolinone (271c). However, in the present work, repetition of this reaction gave only the benzylidene compound (273d) in low yield, in addition to moderate recoveries of both starting materials. None of the quinolinone (271c) was obtained. The benzylidene compound (273d) was also prepared in moderate yield by the piperidine-catalysed condensation of benzoylacetone and 2-nitrobenzaldehyde. Saturation of an ethereal solution of (273d) with hydrogen chloride likewise

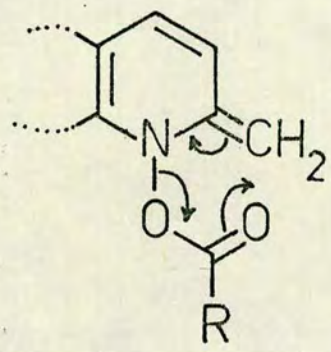
failed to produce the quinolinone (271c). Indane-1,3-dione condensed with 2-nitrobenzaldehyde in the presence of hydrogen chloride to give a moderate yield of a product whose elemental analysis, melting point and mass spectrum showed it to be 2-(2'-nitrobenzylidene)indane-1,3-dione (276).[204] Again, the attempted cyclisation of the latter product using ethereal hydrogen chloride was unsuccessful. The attempted condensation of 2-nitrobenzaldehyde with dimedone in the presence of hydrogen chloride was performed in glacial acetic due to the insolubility of dimedone in ether and was unsuccessful, giving a 63% recovery of dimedone in addition to multi-component mixtures. The attempted condensation of toluene-4-sulphonylacetone[205] with 2-nitrobenzaldehyde in the presence of hydrogen chloride was also unsuccessful yielding only a yellow oil whose t.l.c. showed it to be a mixture of the two starting materials. An attempt was also made to condense 2-nitrobenzaldehyde with ethyl cyanoacetate. The hydrogen chloride-catalysed reaction using glacial acetic acid as solvent produced only a low yield of a colourless solid whose i.r. spectrum contained NH absorption at 3400 and 3120 cm^{-1}, carbonyl absorption at 1705 and 1670 cm^{-1} and absorption at 1530 and 1340 cm^{-1} due to a nitro group indicating that no cyclisation had occurred. The indeterminate melting point of this product and its elemental analysis suggested it to be a mixture of the geometric isomers, (273e) and (273f) of ethyl 2-(2'-nitrobenzylidene)malonamate. No other identifiable material was isolated.

Acetylation of the N-hydroxyquinolinone (271a) gave, in good yield, the known N-acetoxy compound (272a)[202] whose structure was confirmed by its melting point and by the presence in the i.r. spectrum of a high carbonyl absorption (1795 cm^{-1}), characteristic[202]

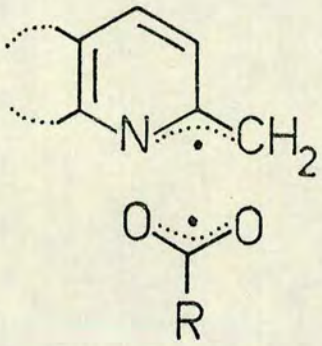
of N-acyloxy compounds. In addition, a small quantity of a brown solid was obtained which was shown by t.l.c. to be a mixture containing the N-acetoxy compound (272a) and one other component. Prolonged treatment of (271a) with acetic anhydride by heating at 100° for six hours produced only a mixture containing (272a) and two other components. The isolation of a mixture in this reaction suggested that the N-acetoxy compound was reacting slowly under the conditions of the acetylation. This was not unexpected due to the previously mentioned similarity in structure between the N-acetoxy compounds (272) and the proposed anhydro base intermediate (cf. 269) in the acetylation reaction of 2-methylquinoline 1-oxide (268). If the N-acetoxy compound (272a) was rearranging in an analogous manner to the proposed anhydro base intermediate (cf. 269) then a likely product would be the 2-acetoxymethylquinolinone (277a). In order to further investigate this rearrangement, the N-acetoxy compound was heated under reflux in glacial acetic acid. On work-up, a crude dark brown solid was obtained. The absence of carbonyl absorption at 1795 cm^{-1} in the i.r. spectrum of this crude solid showed that all of the starting material had been consumed. Extraction of this solid with benzene gave a moderate yield of a pale brown solid whose elemental analysis and mass spectrum showed it to be isomeric with the starting material (272a). The i.r. spectrum showed carbonyl absorption at 1740 cm^{-1} but no absorption at 1795 cm^{-1}. The ^{1}H n.m.r. spectrum showed a singlet at τ 4.68 corresponding to two protons demonstrating the presence of a methylene group. In addition, singlets at τ 7.35 and τ 7.84, each corresponding to three protons, showed the presence of two methyl groups. On the basis of this spectral and analytical data, the pale brown solid is formulated as the acetoxymethylquinolinone (277a). Thus, heating the N-acetoxy

compound (272a) under reflux in glacial acetic acid has caused acetoxylation of the 2-methyl group.

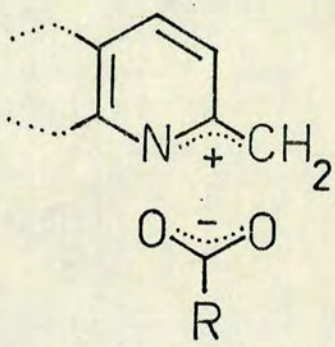
The mechanism of the rearrangement of (272a) is of interest in relation to the reaction of 2-methylquinoline 1-oxide with acetic anhydride. In the latter case, three modes of rearrangement of the anhydro base have been proposed, namely (a) a concerted intramolecular pericyclic rearrangement (130), (b) an intramolecular radical-pair



(130)

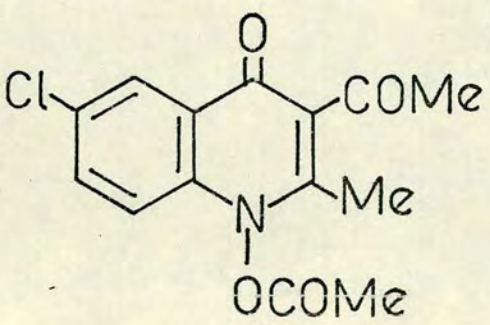


(131)

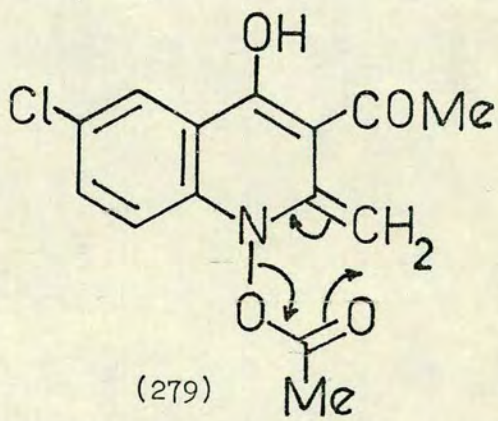


(134)

mechanism (131) and (c) an intramolecular ion-pair mechanism (134) (*cf.* Chapter 1). Similar modes of rearrangement are possible for the conversion of the *N*-acetoxy compound (272a) into the isomer (277a) Thus (272a) might be in tautomeric equilibrium with (279) which is



(272a)



(279)

even more similar to the proposed anhydro base intermediate (*cf.* 269).

As shown, (279) is structurally capable of rearranging *via* a concerted pericyclic mechanism. To investigate this possibility (272a) was heated under reflux in toluene but no rearrangement took place and a quantitative recovery of starting material was obtained. It would appear therefore that the rearrangement cannot be induced thermally and that acid catalysis may be necessary. An attempt to induce the rearrangement of (272a) using ethanolic hydrogen chloride as catalyst was unsuccessful, hydrolysis of the *N*-acetoxy compound (272a) to the *N*-hydroxy compound (271a) occurring instead. This result suggested that specific catalysis by acetic acid is necessary.

An attempt was then made to establish whether or not the rearrangement was intramolecular by means of crossover experiments. The *N*-propionyloxyquinolinone (278) was synthesised in good yield by the reaction of the *N*-hydroxy compound (271a) with propionic anhydride. The structure of (278) was confirmed by its elemental analysis and spectral properties. Its i.r. spectrum showed the high carbonyl absorption (1790 cm^{-1}), characteristic[202] of cyclic *N*-acyloxy compounds and its ^{1}H n.m.r. spectrum was also fully consistent with this structure. Heating the compound (278) at 100° in propionic acid caused rearrangement in a manner exactly analogous to (272a). A dark brown solid was obtained which on leaching with boiling benzene gave a reasonable yield of the 2-propionyloxyquinolinone (277b). This structure is assigned on the basis of elemental analysis and spectral properties. The i.r. spectrum of (277b) showed carbonyl absorption at 1740 cm^{-1}, characteristic of *C*-acyloxy compounds and its ^{1}H n.m.r. spectrum showed the presence of a methylene group (singlet at τ 4.65), an isolated methyl group (singlet at τ 7.32) and an ethyl group (quartet centred at τ 7.52 and a triplet centred at τ 8.84). The crossover experiments were carried

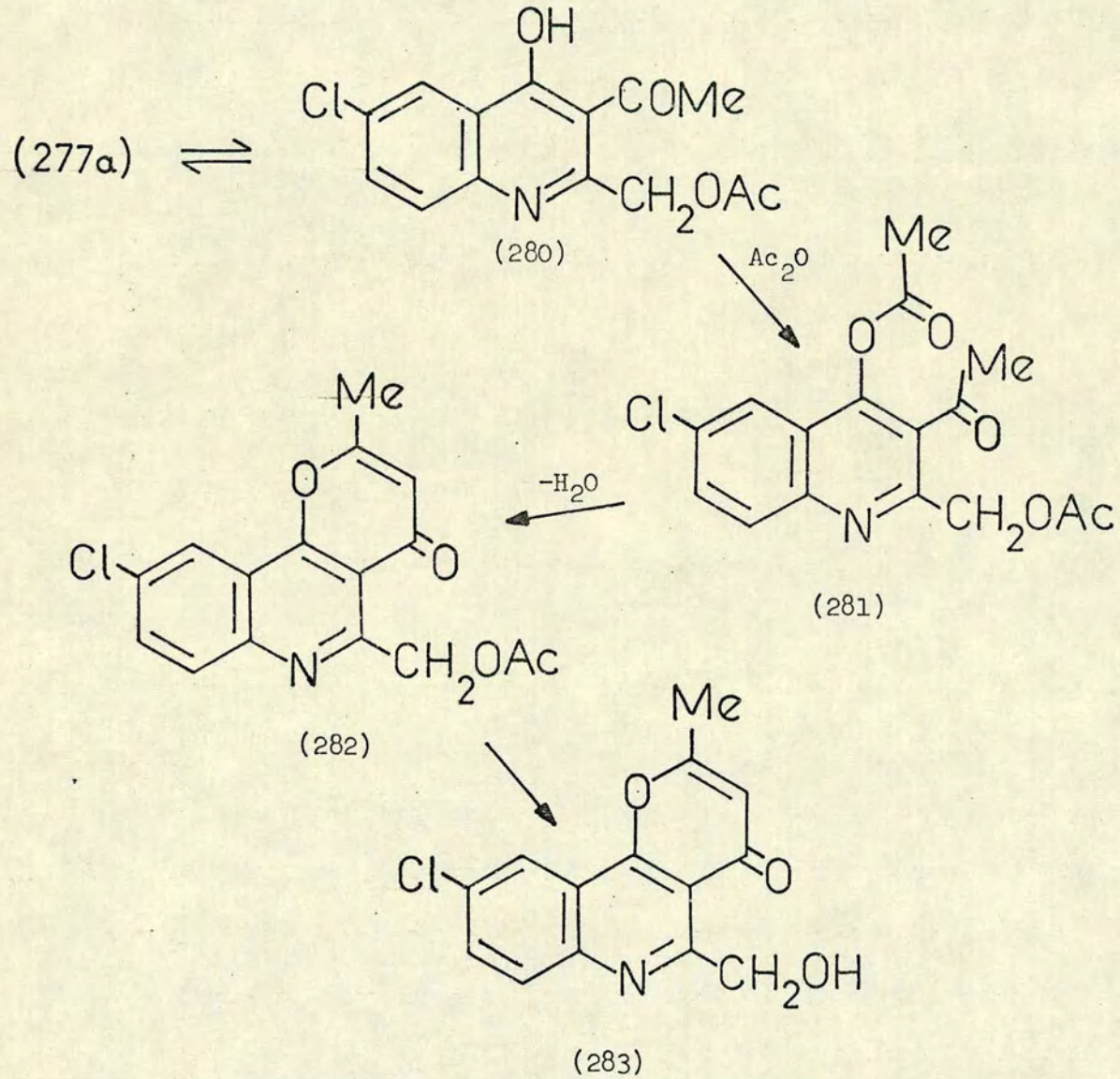
out by heating the N-propionyloxy compound (278) under reflux in glacial acetic acid and by heating the N-acetoxy compound (272a) at 100° in propionic acid. Evaporation of the reaction mixture in the former experiment after 30 min under reflux gave a dark solid which was extracted with boiling benzene to give a pale brown solid in moderate yield. The ^{1}H n.m.r. spectrum of this solid showed it to be a mixture of the 2-acetoxymethylquinolinone (277a) and the 2-propionyloxymethylquinolinone (277b). Comparison of the integral due to the triplet at τ 8.86 [assigned to the methyl substituent of the propionyloxy group in (277b)] with the integral due to the singlet at τ 7.84 [assigned to the methyl substituent in the acetoxy group of (277a)] showed that the mixture contained (277a) and (277b) in the approximate ratio of 1:2.

Heating the N-acetoxy compound (272a) at 100° in propionic acid for 1.75 h gave a low yield of the N-hydroxy compound (271a) showing that some hydrolysis had occurred. In addition a dark solid was obtained which was extracted with benzene to give a pale orange solid in moderate yield. The ^{1}H n.m.r. spectrum of this solid was identical in every respect to the ^{1}H n.m.r. spectrum of the mixture obtained on heating (278) under reflux in glacial acetic acid [i.e. it contained (277a) and (277b) in the ratio 1:2].

The results of these two crossover experiments would, at first sight, seem to demonstrate that the rearrangement of the N-acyloxy compounds (272a) and (278) is at least partly intermolecular since a mixture of the two acyloxymethyl products (277a) and (277b) was formed in each case. However, an unexpected result was obtained when the reaction of the N-acetoxy compound (272a) with propionic acid was interrupted after only 30 min. As in the more prolonged reaction, the N-hydroxy compound (271a) was isolated in low yield from the

reaction mixture. Further work-up produced a brown solid whose indeterminate melting-point indicated it to be a mixture. The i.r. spectrum of this solid showed carbonyl absorption at 1790 and 1740 cm^{-1} suggesting that it was a mixture of the N-acetoxy compound (272a) and either or both of the acyloxymethyl compounds (277a) and (277b). However, examination of its ^1H n.m.r. spectrum at 60 MHz and comparison with authentic spectra of (278) and(277b) showed it to be a mixture of the N-propionyloxyquinolinone (278) and the propionyloxymethyl compound (277b). The singlet at τ 7.30, assigned to the acetyl methyl group of (277b), integrated for 13 units and the singlet at τ 7.37, assigned to the acetyl methyl group of (278), integrated for 26 units. The mixture, therefore, consists of (278) and (277b) in the ratio 2:1. The ^1H n.m.r. spectrum showed no significant amount of either (277a) or (272a). The presence in this mixture of the N-propionyloxy compound (278) and the absence of the starting N-acetoxy compound (272a) shows that prior to the rearrangement acyl exchange has occurred. So, the results of the two crossover experiments must be viewed in terms of this acyl exchange and it is thus not possible to use the results of crossover as a criterion for the molecularity of the rearrangement.

If the rearrangement [(272a) → (277a)] involves an ion-pair mechanism [cf. (134)] and is intermolecular, it should be possible to incorporate nucleophiles other than acetate ion. An attempt was therefore made to perform the rearrangement in the presence of ethanol which could act as a competing nucleophile. Thus,(272a) was heated under reflux in absolute ethanol with one molar equivalent of glacial acetic acid as catalyst. The N-hydroxyquinolinone (271a) was obtained in almost quantitative yield. A small amount of a solid mixture was also isolated from this reaction and was shown by t.l.c. to


(277a)
OH
Cl
COMe
N
CH2OAc
(280)
Ac2O
Me
O
O
Me
O
Cl
N
CH2OAc
(281)
-H2O
Me
O
Cl
O
N
CH2OAc
(282)
Me
O
Cl
O
N
CH2OH
(283)

Scheme 21

comprise the N-hydroxy compound (271a), the acetoxymethyl compound (277a) and a trace of a third unidentified component. There was no evidence of the incorporation of ethanol and hence of an intermediate cation.

An attempt was also made to perform the rearrangement in the presence of chloride ion. Since a mixture of acetyl chloride and glacial acetic acid is a convenient source of an acylating agent and chloride ion, the N-hydroxy compound (271a) was heated with these reagents. The N-acetoxy compound (272a) was thus formed *in situ*. As in the other reactions leading to rearrangement, a brown solid was obtained which was extracted with light petroleum to give a moderate yield of an orange solid whose t.l.c. showed it to be a two component mixture comprising the 2-acetoxymethyl compound (277a) and a second yellow fluorescent compound. An attempt was made to separate this mixture by column chromatography over alumina. However, the only pure component obtained in low yield was a yellow fluorescent solid whose elemental analysis and mass spectrum suggested the molecular formula $C_{14}H_{10}ClNO_3$. Its i.r. spectrum showed hydroxyl absorption (3150 cm^{-1}) and carbonyl absorption (1640 cm^{-1}). These data are consistent with the pyrano[3,2-c]quinoline structure (283). The formation of this compound can be explained as shown in Scheme 21. Initially, (277a) is formed by rearrangement of the N-acetoxy compound (272a). Acetylation of the 4-hydroxy tautomer (280) of the quinolinone (277a) then produces the 4-acetoxyquinoline (281), dehydrative cyclisation of which gives the pyrano[3,2-c]quinoline (282) convertible into (283) by hydrolysis. The remainder of the fractions isolated from the column were found by t.l.c. to be inseparable mixtures which did not contain the acetoxymethyl compound (277a). It would appear therefore that

hydrolysis and possibly further reaction had occurred on the column. There was no evidence that chloride ion had been incorporated into any of the products.

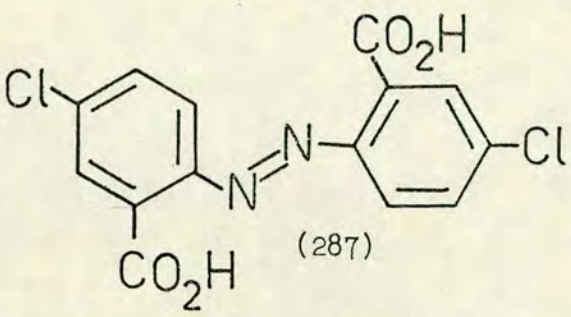
The failure of other nucleophiles to interfere with the course of the rearrangement of N-acyloxyquinolinones may be explained in a number of ways. The mechanism of the rearrangement may not involve an ion-pair, although all the evidence gathered in the analogous acylation reactions of α-methyl N-oxides (see Chapter 1, pp. 20-21) strongly supports the involvement of ions. On the other hand, if the ion-pair mechanism is involved, then heterolytic cleavage of the N-O bond may be slow followed by rapid ion-pair return before any other nucleophile can interfere. If rapid ion-pair return is involved, then cleavage of the N-O bond will be facilitated by making the acyloxy moiety into a better leaving group, i.e. by increasing the stability of the acyloxy anion. This will also discourage ion-pair return and increase the chance of competitive attack by other nucleophiles. The tosyloxy group is a better leaving group than the acetoxy group and also a poorer nucleophile. Consequently, an investigation of the reactions of the N-hydroxyquinolinones (271 a and b) with sulphonyl chlorides was undertaken.

The room temperature reaction of the N-hydroxy compound (271a) with tosyl chloride in pyridine gave a moderate yield of a colourless solid, (X), whose elemental analysis and mass spectrum showed it to have the molecular formula $C_{17}H_{14}Cl\ NO_4S$. The ^1H n.m.r. spectrum of (X) showed the presence of seven aromatic protons (four of which could be attributed to a tosyl group) and two methyl groups. In addition to (X), a 21% yield of the N-acetoxy compound (272a) and a 16% recovery of the starting N-hydroxy compound (271a) were obtained.

The reaction of the 3-ethoxycarbonyl-1-hydroxyquinoline (271b) with tosyl chloride in pyridine gave a very low yield (5%) of the same colourless solid, (X). Also isolated in this reaction was a low yield of a pale brown salt which on basification and extraction gave an unidentified orange solid. The remainder of the recovered material consisted of intractable multi-component oils.

The isolation of the same solid, (X), from the reactions of both the 3-acetylquinoline (271a) and the 3-ethoxycarbonylquinoline (271b) with tosyl chloride in pyridine indicates that its formation must involve the replacement of the group at the 3-position. Replacement of the 3-acetyl group in the reaction of (271a) with tosyl chloride in pyridine is confirmed by the isolation of the N-acetoxyquinoline (272a) (see Scheme 22 and p. 112). Three structures for (X) are consistent with these results and with its molecular formula, namely (284), (285) and (286). The N-hydroxy structure (284) may be discounted since, although (X) is soluble in alkali, it does not give a colour in the presence of iron (III) chloride. Also, the attempted acetylation of (X) was unsuccessful whereas it would be expected that structure (284) should acetylate readily. The attempted methylation of (X) also proved difficult. Treatment of (X) with sodium hydroxide solution with warming to ensure formation of the sodium salt and subsequent shaking with dimethyl sulphate gave only a quantitative recovery of the starting material (X). However, methylation of (X) with methyl iodide in dry dimethylformamide using sodium hydride as base gave a product of formula $C_{18}H_{16}ClNO_4S$ showing that (X) contains one methylatable centre. The ^1H n.m.r. spectrum of the methylated product showed, in addition to signals similar to those of the two methyl groups in (X), a three proton singlet at τ 5.62, consistent with the presence of an O-methyl group rather than an N-methyl group the protons of which would resonate at higher field.

A known[202] reaction of quinolin-4(1H)-ones and the corresponding N-hydroxy compounds is their oxidation in chromic acid to substituted azobenzenes and azoxybenzenes. For instance, oxidation of a derivative of 6-chloroquinolin-4(1H)-one would be expected to yield the substituted azobenzene (287) while the corresponding N-hydroxy compound should



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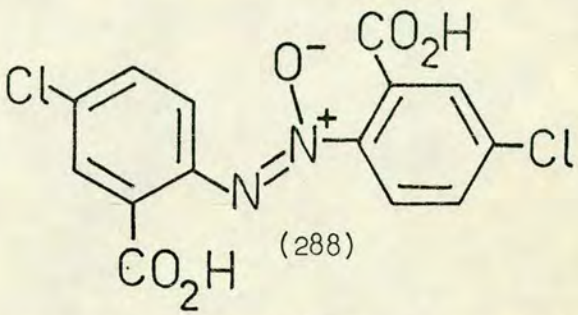


(288)

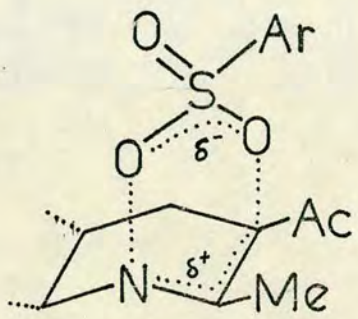
yield the azoxybenzene (288). To determine whether (X) still contained the 6-chloroquinolinone nucleus or whether a more involved reaction had occurred in the formation of (X) it was heated under reflux with sodium dichromate in acid solution. A 75% recovery of starting material was obtained and no other identifiable material was isolated.

An attempt was next made to degrade the unknown compound, (X), to some identifiable material by alkaline hydrolysis. Using relatively strong aqueous potassium hydroxide, a 25% recovery of the starting material was obtained, the remainder of the material isolated being intractable gums. Heating (X) with potassium hydroxide in trigol resulted in extensive decomposition yielding dark multi-component oils. It seemed unlikely therefore that (X) had the structure (285) since such a tosylate should be easily hydrolysed and would be unable to withstand forcing alkaline hydrolysis or the acidic conditions used in the attempted oxidation. The third possible structure (286) however contains an N-tosyl substituent which would be relatively stable thus accounting for the lack of reactivity of (X) towards attempted oxidation. Also, such sulphonamides are somewhat resistant

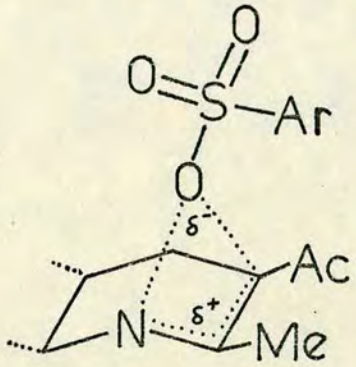
to hydrolysis. An N-tosyl group may however be removed reductively.[206] Reduction of (X) using sodium in liquid ammonia gave a reasonable yield of the known[207] compound 3-hydroxy-2-methylquinolin-4(1H)-one (289a) whose structure was confirmed by comparison with an authentic sample. Thus, under these conditions reductive removal of the 6-chloro substituent as well as the N-tosyl group occurs.

The spectral and analytical properties of (X) and its conversion by reduction into the known[207] quinolinone (289a) are all consistent with the 6-chloro-3-hydroxy-2-methyl-1-(toluene-4'-sulphonyl)quinolin-4(1H)-one structure (286). It follows that the methylated derivative is the 3-methoxyquinolinone (290). The formation of (286) from the N-hydroxy compound (271a) on treatment with tosyl chloride in pyridine may be explained as shown in Scheme 22. Initial tosylation of the N-hydroxy group would give the N-tosyloxyquinolinone (291) which could then rearrange to (292) as shown. Such 1,3-migrations of a tosyloxy group across an allylic-type system are common and have frequently been proposed as intermediate steps to explain β-substitution in the reactions of N-oxides with tosyl chloride (cf. Chapter 1, p.22). The reaction of isoquinoline N-oxide (121) with tosyl chloride to give 4-tosyloxyisoquinoline (144) has been studied[208] using ^{18}O labelled tosyl chloride and the mechanism shown in Scheme 23 has been proposed. Since there is no incorporation of ^{18}O isotope into the ether-linked oxygen of the product (144), it is thought that the rearrangement [(295) → (297)] occurs via a concerted "slither" migration of the tosyloxy group as shown (296). However, this could also be explained in terms of heterolytic fission of the N-O bond of (295) followed by fast ion-pair return before equilibration of the oxygen atoms of the tosylate anion could occur.

In the mechanism (Scheme 22) proposed for the formation of (286) by the reaction of (271a) with tosyl chloride in pyridine, the rearrangement [(291) → (292)] may be a concerted process, either *via* a six-membered transition state (298) or by a concerted "slither" mechanism (299). Alternatively, radical-pairs or ion-pairs may be involved. Without further work, it is impossible to say which mechanism is involved in



(298)



(299)

the rearrangement, [(291) → (292)].

Subsequent nucleophilic attack on (292) would then remove the acetyl group to form the anion (293). The nucleophile involved may be the starting *N*-hydroxy compound (271a) or, more likely, the solvent pyridine. The *N*-acetylpyridinium ion formed could then react with the starting material to form the *N*-acetoxy compound (272a) which was also isolated. Reaction of the anion (293) with a further molecule of tosyl chloride followed by hydrolysis of the *C*-tosyloxy group then explains the formation of the product (286). This mechanism (Scheme 22) involves two molecules of tosyl chloride for every one molecule of the *N*-hydroxy compound. Performing the reaction using two molar equivalents of tosyl chloride unexpectedly gave a decrease in the yield of (286). In addition, a small amount of a colourless salt was obtained which yielded an unidentified yellow solid on dissolving in water and basifying with solid sodium bicarbonate (*cf.* p. 115).

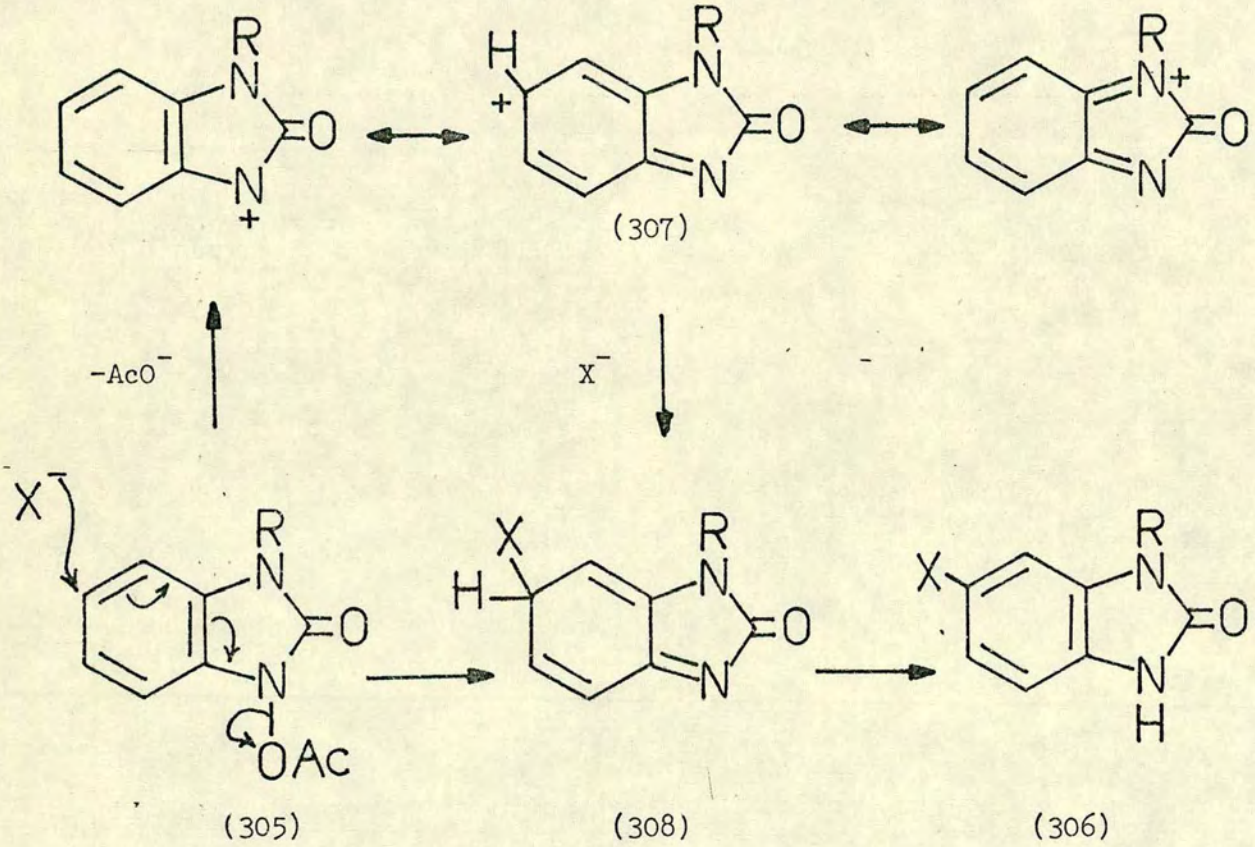
If the tosylation of (271a) was carried out under neutral conditions, then the anion (293) would be rapidly neutralised and the second tosylation step would be prevented. Heating (271a) under reflux in dimethylformamide with tosyl chloride gave a moderate yield of the known[207] 6-chloro-3-hydroxyquinolin-4(1H)-one (289b) whose structure was confirmed by comparison with an authentic sample.

As mentioned previously, the rearrangement of (291) to (292) may occur *via* an ion-pair mechanism. If this is the case, then it might be possible to intercept the cation by carrying out the reaction in the presence of other nucleophiles. With this aim in view, the reaction of (271a) with tosyl chloride in pyridine was repeated but with the addition of a four-fold excess of powdered sodium cyanide. The yield of (286) was unaffected but a substantially increased recovery of starting material was obtained. There was also no trace of the *N*-acetoxy compound (272a). It would appear that the cyanide ion does not interfere with the rearrangement of (291) but does act as the nucleophile which removes the acetyl group from (292), thus preventing formation of the *N*-acetoxy compound (272a).

Another attempt to divert the rearrangement [(291) → (292)] was made using methanol as the nucleophile. Tosyl chloride was added at -40° to a solution of (271a) and *tri*ethylamine in dimethylformamide and after a few minutes the solution was quenched with methanol. This reaction was carried out at low temperature because at room temperature decomposition with the formation of multi-component mixtures occurred. It was hoped that at low temperature the rate of the rearrangement would be sufficiently slow to allow the methanol to become involved. However, on work-up a good yield of the quinolinone (286) was obtained in addition to a small amount of starting material. There was no evidence for the involvement of methanol in the reaction.

As an extension of the sulphonylation reaction of (271a), methanesulphonyl chloride was used in place of tosyl chloride. A colourless solid, analogous to (286) was obtained in low yield. Elemental and mass spectral analysis showed a molecular formula of $C_{11}H_{10}Cl\ NO_4S$. The i.r. spectrum of the product showed a broad band at 3100-2600 cm^{-1} assigned to hydroxyl absorption and no acetyl absorption. The ^1H n.m.r. spectrum showed signals due to three aromatic protons and two methyl groups. On the basis of analytical and spectral data and by analogy with the structure (286), this product is assigned the 1-methanesulphonylquinoline structure (300). In addition to (300), the reaction of (271a) with methanesulphonyl chloride gave a second colourless solid, also in low yield. The elemental analysis and mass spectrum of this product suggested the molecular formula $C_{13}H_{12}Cl\ NO_5S$. The i.r. spectrum showed a broad band at 3200-2600 cm^{-1} assigned to NH absorption and a carbonyl band at 1700 cm^{-1} showing retention of the acetyl group. The ^1H n.m.r. spectrum contained two doublets each integrating for one proton, centred on τ 1.45 and τ 1.85 respectively, with a common coupling constant ($J = 2$ Hz). These are assigned to two isolated meta-coupled aromatic protons. Three singlets at τ 6.44, 6.68 and 7.04, each integrating for three protons are assigned to the methanesulphonyl group, the 2-methyl group and the acetyl group respectively. On this basis, the second product is formulated as the 8-methanesulphonyloxyquinolinone (301). In addition to the two products (300) and (301) a small amount of a colourless salt was obtained which on dissolving in water, basifying and extracting into chloroform yielded a bright yellow solid. The melting point and i.r. spectrum of this compound were identical to those of the yellow solid isolated from the reaction of two molar

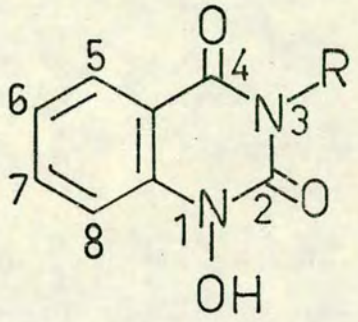
equivalents of tosyl chloride with (271a) (cf. p. 112). The elemental analysis and mass spectrum of the yellow solid could not be fitted to a molecular formula and the low yield obtained prevented any further investigation of this product. However, the ^{1}H n.m.r. spectrum of this solid contained three groups of multiplet signals in the aromatic region, the integral corresponding to eight protons, and a three proton singlet at τ 7.42 assigned to the 2-methyl group. The lack of carbonyl absorption around 1700 cm^{-1} in the i.r. spectrum confirms the absence of the acetyl group. The bright colour of the product and its ability to form colourless salts readily on treatment with acid, as well as analogy with similar compounds formed in the quinoxaline series (cf. Chapter 4, Part 3), tentatively suggest that this yellow solid may have the betaine structure (302). The formation of the betaine (302) would be readily explained by competing reaction of the N-tosyloxy compound (291) with pyridine. However, in the absence of any other evidence, this must remain a tentative suggestion. A similar solid was isolated in low yield from the reaction of the 3-ethoxycarbonyl compound (271b) with tosyl chloride in pyridine (cf. p. 109) but this solid could not be crystallised for characterisation.



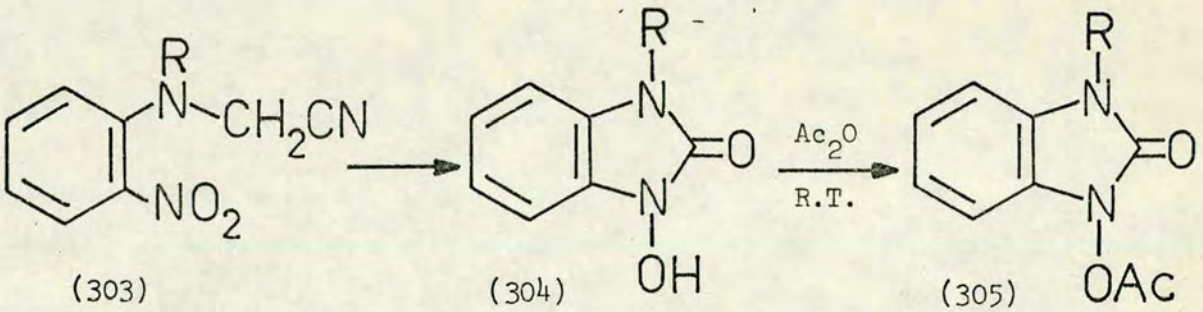
(305) (308) (306)

Scheme 24

Part 2. 1-Hydroxy-quinazoline-2(1H),4(3H)-diones



N-Hydroxybenzimidazolinones (304), which are readily available by the base-catalysed cyclisation of N-cyanomethyl-2-nitroanilines (303), show unusual reactivity in the presence of acylating agents[191]. The reaction of (304) with acetic anhydride at room temperature affords



the expected N-acetoxy compounds (305). However, at elevated temperatures, the reaction proceeds further yielding 5-acetoxy-benzimidazolinones (306; X=OAc). In addition, heating the N-hydroxy compounds (304) with acylating agents in the presence of a variety of nucleophilic reagents results in the general formation of 5-substituted benzimidazolinones (306)[209]. These findings may be explained by either of two possible mechanisms (Scheme 24). A concerted mechanism involving nucleophilic attack on the N-acetoxy compound (305) with concomitant loss of acetate ion could afford the intermediate (308) which on prototropic rearrangement would yield the observed product (306). Alternatively, formation of the intermediate (308) could occur in a stepwise fashion via a resonance-stabilised nitrenium ion (307) formed by heterolytic cleavage of the N-O bond

in (305). 1-Hydroxyquinoxaline-2(1H),3(4H)-diones (309) (cf. Part 3) and 1-hydroxyquinazoline-2(1H),4(3H)-diones (311) are structurally similar to the N-hydroxybenzimidazolinones (305) and might be expected to undergo similar transformations in the presence of acylating agents. So, it was decided to study the acylation reactions of these analogous six-membered ring heterocycles [(309) and (311)].

With this objective in mind, a series of 1-hydroxyquinazolinediones (311 a-d) was synthesised by the well-known[210] base-catalysed cyclisation of the corresponding N,N-disubstituted 2-nitrobenzamides (310 a-d). The amides (310 a-c) were prepared in good yield using the literature methods[210] involving the condensation of 2-nitrobenzoyl chloride with N-methylaminoacetonitrile hydrochloride, N-benzylaminoacetonitrile[211] and anilinoacetonitrile[212] respectively. The amide (310d) was likewise prepared in good yield by the condensation of 5-chloro-2-nitrobenzoyl chloride[213] with anilinoacetonitrile in the presence of anhydrous potassium carbonate. The structure of the amide (310d) is assigned on the basis of elemental analysis and i.r., ^{1}H n.m.r. and mass spectral data.

The amides (310 a-c) were cyclised using sodium ethoxide to give the known[210] N-hydroxy compounds (311 a-c) in high yield. Similar treatment of the amide (310d) afforded 6-chloro-1-hydroxy-3-phenylquinazoline-2(1H),4(3H)-dione (311d) in good yield. The structure (311d) for this product is fully consistent with its elemental analysis and its i.r. and mass spectra. In addition, the compound (311d) gave a purple colour in the presence of iron (III) chloride, as did compounds (311 a-c), behaviour characteristic[210] of N-hydroxy compounds.

Mild treatment of the N-hydroxyquinazolines (311 a-c) with acetic anhydride has been shown[210] to afford the corresponding N-acetoxy compounds (312 a-c). It was thought that prolonged treatment with acetic anhydride might result in a rearrangement analogous to that

reported for the benzimidazole series [cf. (305) → (306; X=OAc)]. However, heating the compound (311b) with acetic anhydride at 100° for 4 h afforded an almost quantitative yield of the known[210] N-acetoxy compound (312b). The absence of any other products shows that cleavage of the N-O bond in (312b) has not occurred under these conditions. The presence of a better leaving group than acetoxy might be expected to weaken and hence encourage heterolytic cleavage of the N-O bond. Since a tosylate substituent is an excellent leaving group, a study of the reactions of the N-hydroxy compounds (311 a-d) in the presence of sulphonyl halides was undertaken.

The reaction of the N-hydroxyquinazoline (311c) with tosyl chloride in dimethylformamide at 100° produced only an unresolvable multi-component mixture. On the other hand, room temperature reactions of the N-hydroxy compounds (311 a-d) with tosyl chloride were much more successful. The reaction of (311a) in dry dioxan with tosyl chloride in the presence of triethylamine gave a high yield of a colourless solid whose elemental analysis and mass spectrum indicated the molecular formula $C_{16}H_{14}N_2O_5S$. The solid was only crystallised once prior to analysis since prolonged heating in organic solvents caused rearrangement (see later). The product also exhibited interesting melting behaviour. After melting at 121°, the melt resolidified with further melting over the range 170-195°. This behaviour will be discussed in detail later. The i.r. spectrum of the product showed no OH or NH absorption and its ^1H n.m.r. spectrum contained a two proton doublet (J_{ortho} 8 Hz) at τ 2.01 and a three proton singlet at τ 7.52 demonstrating the presence of a tosyl group. The molecular formula and spectral properties of the colourless solid are consistent

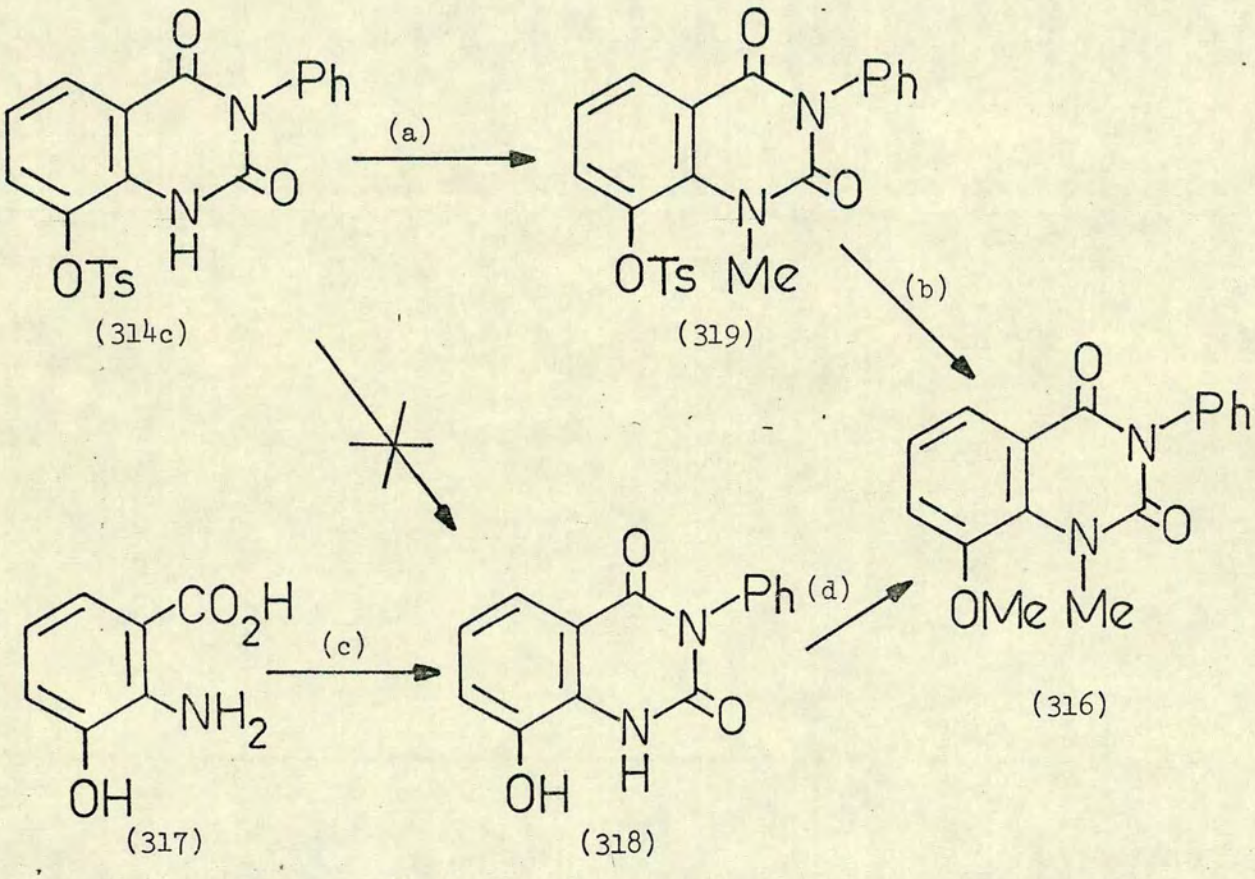
with the N-tosyloxyquinazoline structure (313a). This structure was confirmed by hydrolysis of the colourless solid in dilute aqueous sodium hydroxide to give, in addition to unreacted starting material, a good yield of the N-hydroxyquinazolinedione (311a).

The N-hydroxy compounds (311 b and c) also reacted readily with tosyl chloride in dioxan in the presence of triethylamine to give high yields of the N-tosyloxy compounds (313 b and c), respectively. The compounds (313 b and c) gave elemental analyses and spectral data fully consistent with the assigned structures. The N-methanesulphonyloxyquinazoline (313d) was likewise prepared by the reaction of the N-hydroxyquinazolone (311a) with methanesulphonyl chloride in the presence of triethylamine. In this case, a small quantity of the starting material (311a) was also recovered. The i.r. spectrum of (313d) contained no OH or NH absorption and its ^{1}H n.m.r. spectrum showed four aromatic protons and two methyl groups, consistent with the structure (313d).

The N-sulphonyloxyquinazolines (313 a-d) all appeared to rearrange on prolonged heating in organic solvents and so were crystallised only once prior to analysis. In addition, they all melted sharply, followed by resolidification with subsequent melting over a long temperature range. This unusual melting behaviour was studied by heating the solid N-sulphonyloxy compounds (313 a-d) in a cold-finger sublimation apparatus under reduced pressure at the melting point and re-examining the cooled melt. The glassy solid obtained by heating (313c) was shown by t.l.c. to be a two component mixture which was separated into its components by preparative t.l.c. The two components, neither of which corresponded to the tosylate (313c), were shown by mass spectral and elemental analysis to be isomeric with the starting material. The presence of a tosyloxy group in both isomers is supported by their elemental analyses and confirmed by their ^{1}H n.m.r.

spectra which contain the four-proton A_2X_2 pattern characteristic of a para-substituted tosyl group. However, their i.r. spectra contain broad bands around 3000 cm^{-1} attributable to the presence of NH absorption. It follows that the tosyloxy groups can no longer be attached to the ring nitrogen atom and must therefore be situated on the fused benzene ring. The ^1H n.m.r. spectra of both isomers confirms this since each shows only a total of twelve aromatic protons, comprising the five protons of the N-phenyl group, the four protons of the tosyl group and only three protons due to the fused benzene ring. In addition, the ^1H n.m.r. spectrum of the major component showed as the lowest aromatic signal a one-proton double doublet (J_{meta} 2 Hz and J_{ortho} 8 Hz) at τ 1.81. Since the most deshielded aromatic proton must be that at C-5, adjacent to the C-4 carbonyl group, the splitting pattern associated with this proton demonstrates the absence of substituents at C-6 and C-7 and this allows the assignment of the 8-tosyloxy structure (314c) to the major isomer produced by the thermal rearrangement of the tosylate (313c). The ^1H n.m.r. spectrum of the minor isomer could not be analysed satisfactorily thus precluding the determination of the site of attachment of the tosyloxy group in this product. However, by analogy with the rearrangement of the N-acetoxybenzimidazole [(305) → (306; X=OAc)], it would seem likely that the minor product from the thermal rearrangement of the tosylate (313c) has the 6-tosyloxyquinazolinedione structure (315c).

The structure of the major product (314c) of the thermal rearrangement of the tosylate (313c) was subsequently verified by its conversion by methylation followed by hydrolysis and further methylation (Scheme 25) into the 8-methoxyquinazoline (316) which was synthesised unambiguously from 3-hydroxyanthranilic acid (317)



a) Me_2SO_4 - Acetone

b) aq. NaOH followed by Me_2SO_4

c) PhNCO

d) Me_2SO_4 - aq. NaOH

Scheme 25

as shown (Scheme 25). An attempt to hydrolyse the tosylate (314c) directly to the 8-hydroxyquinazolinedione (318) using aqueous sodium hydroxide was unsuccessful, resulting in extensive decomposition of the starting material. Consequently, (314c) was first methylated using dimethyl sulphate in dry acetone to give a good yield of the 1-methylquinazoline (319) whose structure is assigned on the basis of its elemental analysis and mass, i.r. and ^{1}H n.m.r. spectra. In addition, this reaction gave a small amount of a solid whose ^{1}H n.m.r. spectrum showed it to be a mixture containing the N-methyl derivative (319) but mainly comprising a second unidentified component as demonstrated by the presence of an additional methyl signal at τ 6.17. The 8-tosyloxy compound (319) was hydrolysed and methylated in one step using dilute aqueous sodium hydroxide followed by dimethyl sulphate to give the 8-methoxy-1-methylquinazoline (316) whose structure is based on mass spectral and elemental analysis and its i.r. spectrum, which lacks OH and NH absorption. This product was shown by melting point, mixed melting point and i.r. spectrum to be identical to a sample of (316) synthesised from 3-hydroxyanthranilic acid (317). Treatment of (317) in dry dimethylformamide with phenylisocyanate gave a low yield of solid whose elemental analysis and mass spectrum indicated the molecular formula, $C_{14}H_{10}N_2O_3$, which together with the i.r. spectrum supports the structure (318). Methylation of (318) using aqueous sodium hydroxide and dimethyl sulphate gave (316), thus confirming the 8-tosyloxy structure (314c) for the major product of the thermal rearrangement of (313c).

The thermal rearrangement of the N-methanesulphonyloxy compound (313d) gave a two component mixture which was readily separated by preparative t.l.c. As in the rearrangement of (313c), both products were found to be isomeric with the starting material and their i.r. and ^{1}H n.m.r. spectra showed that both compounds were 3-methylquinazoline-

2(1H),4(3H)-diones containing a methanesulphonyloxy substituent in the benzene ring. The ^{1}H n.m.r. spectra of the two isomers were however sufficiently simple to permit the complete assignment of the aromatic signals and hence to establish the substitution pattern in the benzene ring. The lowest field signal at τ 2.09 in the ^{1}H n.m.r. spectrum of the major product (the faster-moving component on t.l.c.) can be assigned to H-5 which is deshielded by the adjacent C-4 carbonyl group and appears as a double doublet due to ortho-coupling (J 8 Hz) and meta-coupling (J 2 Hz). The signal at τ 2.78 appears as a triplet showing coupling (J 8 Hz) to two ortho-protons and so, is assigned to H-6. The third aromatic signal at τ 2.36 is assigned to H-7 since it appears as a double doublet demonstrating ortho-coupling (J 8 Hz) with H-6 and meta-coupling (J 2 Hz) with H-5. Thus, the methanesulphonyloxy substituent is sited at C-8 and the major product from the rearrangement of (313d) is assigned the 8-methanesulphonyloxy structure (314d).

In contrast, in the ^{1}H n.m.r. spectrum of the minor component (the slower-moving component in t.l.c.), the lowest aromatic signal at τ 2.18 appears as a doublet, showing meta-coupling (J 2 Hz). This signal is assigned to the 5-proton, since being adjacent to the carbonyl group at C-4,it is most deshielded. Since this signal shows no ortho-coupling,the 6-position must be substituted. This is confirmed by the presence of a signal at τ 2.36 which appears as a double doublet, showing meta-coupling (J 2 Hz) to H-5 and ortho-coupling (J 9 Hz) to only one proton. This signal is assigned to H-7 since it is meta-coupled to H-5. The remaining aromatic signal, which appears as a doublet (J_{ortho} 9 Hz) due to ortho-coupling with H-7,is assigned to H-8 , the lack of meta-coupling in H-8 again demonstrating the presence of a C-6 substituent. It follows that the minor product of the thermal rearrangement of (313d) has the

6-methanesulphonyloxy structure (315d). This assignment also provides additional support for the formulation of the minor product of the thermal rearrangement of (313c) as the 6-tosyloxyquinazoline (315c).

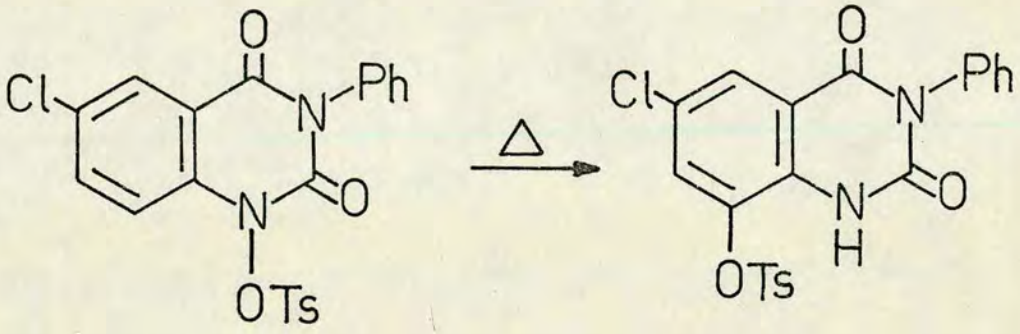
The thermal rearrangement of the N-benzyl compound (313b) also gave two products, isomeric with the starting material (313b), which were separated by preparative t.l.c. The i.r. spectra of both products showed NH absorption and their ^{1}H n.m.r. spectra, which were too complex to permit the assignment of individual protons, showed the presence of twelve aromatic protons confirming that substitution in the fused ring had occurred. By analogy with the thermal rearrangements of (313c) and (313d), the major product (the faster-moving component in t.l.c.) is assigned the 8-tosyloxy structure (314b) and the minor product is assigned the 6-tosyloxy structure (315b).

The major product from the thermal rearrangement of the N-methyl compound (313 a) was, as in the thermal rearrangements of (313 b-d), isomeric with the starting material (313a). The ^{1}H n.m.r. spectrum of this product contained a one-proton signal at τ 2.85 which appeared as a triplet (J 8 Hz). The proton producing this signal must therefore be coupled to two ortho-protons and the two positions meta to this proton must be substituted. Thus, in the fused benzene ring, the three protons must be adjacent i.e. the 5- or 8-position must be substituted. By analogy with the rearrangements of (313 b-d), this product is assigned the 8-tosyloxy structure (314a). Similarly the minor product, also isomeric with (313a), is assigned the 6-tosyloxy structure (315a). The ^{1}H n.m.r. spectrum of this product was too complex in the aromatic region to permit the assignment of individual protons.

The thermal rearrangement of the N-methyl compound (313a) could also be effected in solution by heating under reflux in

glacial acetic acid or tetrahydrofuran. T.l.c. of the solid obtained showed it to be a mixture of (314a) and (315a), identical to the mixture obtained from the thermal rearrangment in the absence of solvent except for a trace of a third, slower-moving component which may have been the result of hydrolysis of the products by water in the solvents.

The thermal rearrangements of the N-sulphonyloxy compounds (313 a-d) all produced mixtures of the 8-sulphonyloxy compounds (314 a-d) and the 6-sulphonyloxy compounds (315 a-d), the former compounds always being the major product. It was thought that thermal rearrangement of an N-tosyloxyquinazoline carrying a substituent (e.g. chlorine) in the 6-position would proceed smoothly to afford only an 8-tosyloxy

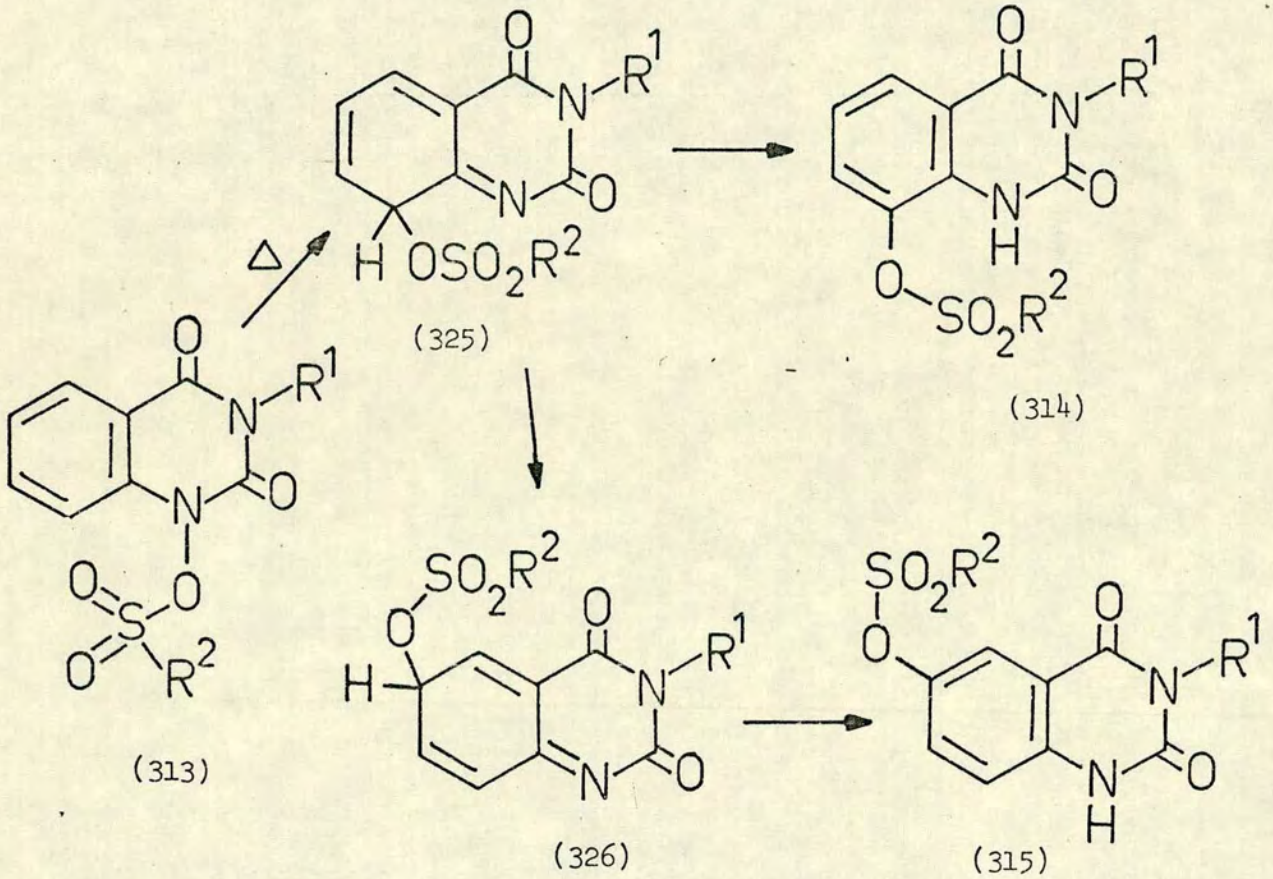


(320) (321)

compound. Consequently, the 6-chloro-1-tosyloxyquinazoline (320) was prepared in high yield by the room temperature reaction of the N-hydroxy compound (311d) with tosyl chloride in the presence of triethylamine. The structure (320) proposed for the product of this reaction is assigned on the basis of its elemental analysis and spectral properties and also by analogy with the formation of the N-sulphonyloxy compounds (313 a-d) formed under similar conditions. Like the compounds (313 a-d), the tosylate (320), on heating, melted, resolidified and further melted over a range of about 15° suggesting that thermal rearrangement was occurring. Under the identical conditions

used for the rearrangements of (313 a-d), the thermal rearrangement of (320) afforded,after crystallisation,a good yield of the 6-chloro-8-tosyloxyquinazoline (321). T.l.c. of the solid obtained by evaporation of the crystallisation liquors showed it to be a multi-component mixture, indicating that the rearrangement had not proceeded as cleanly as expected. The structural assignment (321) for the rearranged product is based on its elemental analysis and spectral data. The i.r. spectrum showed broad absorption at 3100-2600 cm^{-1} and the ^1H n.m.r. spectrum contained a broad singlet at τ 1.58, indicating the presence of a free NH group. Also, the ^1H n.m.r. spectrum showed only eleven aromatic protons suggesting that the tosyloxy group was now sited on the benzene ring. On mechanistic grounds (Scheme 26) and by analogy with the rearrangements of (313 a-d), the most likely position of substitution is at the 8-position.

It also seemed reasonable to suppose that the rearrangement of an N-tosyloxy compound carrying a substituent at C-8 would result in an increased yield of the 6-tosyloxy product by preventing formation of the 8-tosyloxy isomer. Consequently an attempt was made to synthesise the 8-methyl-1-tosyloxyquinazoline (322). The amide (323) was prepared in almost quantitative yield by the condensation of N-methylaminoacetonitrile hydrochloride with 3-methyl-2-nitrobenzoyl chloride[214] which was prepared in quantitative yield by the action of phosphorous pentachloride on 3-methyl-2-nitrobenzoic acid. Cyclisation of the amide (323) using ethanolic sodium ethoxide gave a moderate yield of the N-hydroxyquinazoline (324) which gave analytical and spectral data consistent with the structure (324). Its i.r. spectrum showed a broad band at 3100 cm^{-1} characteristic of an N-hydroxy group. The aromatic region of its ^1H n.m.r. spectrum was sufficiently well resolved to permit the assignment of the signals to the individual aromatic protons.



	R^1	R^2
a)	Me	p-tolyl
b)	CH_2Ph	p-tolyl
c)	Ph	p-tolyl
d)	Me	Me
e)	H	p-tolyl

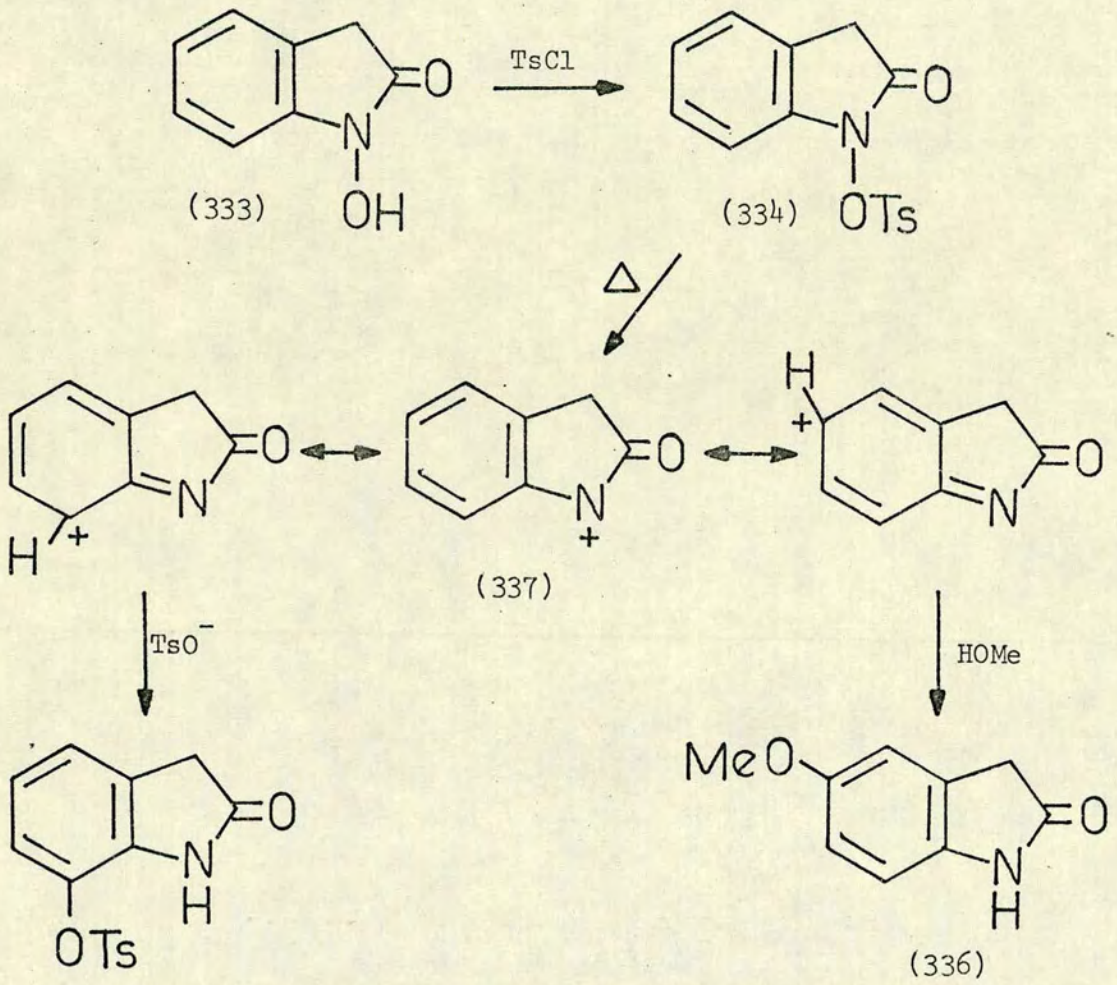
Scheme 26

The signal assigned to H-5 appears as a double doublet centred at τ 2.13, showing ortho-coupling (J 8 Hz) to H-6 and meta-coupling (J 2 Hz) to H-7. The signal assigned to H-6 appears as a triplet centred at τ 2.89, showing ortho-coupling (J 8 Hz) to both H-5 and H-7, while the remaining signal was also a double doublet centred at τ 2.50, showing ortho-coupling (J 8 Hz) with H-6 and meta-coupling with H-5, and is therefore assigned to H-7. Unfortunately, the attempted synthesis of the N-tosyloxy compound (322) was unsuccessful. The reaction of the N-hydroxy compound (324) with tosyl chloride in the presence of triethylamine, both at room temperature and at -10°, produced only multi-component mixtures.

The formation of the products (314) and (315) in the thermal rearrangement of the N-sulphonyloxyquinazolines (313) may be explained by the mechanism proposed in Scheme 26. A formal 1,3-shift of the sulphonyloxy group from N-1 to C-8 affords the non-aromatic intermediate (325) which may then further react by either of two different routes to afford the two different products (314) and (315). The 8-sulphonyloxy compound (314) is formed directly from the intermediate (325) by a rapid proton shift, the driving force for this step being the rearomatisation of the benzene ring. Alternatively, (325) may undergo a second formal 1,3-shift of the sulphonyloxy group from C-8 to C-6 giving a second non-aromatic intermediate (326) which may rearomatise via a proton shift to give the 6-sulphonyloxy compound (315). This latter product is not formed directly from the 8-sulphonyloxy isomer (314) since the attempted rearrangement of (314a) under the same conditions used for the rearrangements of (313 a-d) gave a quantitative recovery of the starting material (314a).

The mechanism shown in Scheme 26 to explain the formation of the two products (314) and (315) by rearrangement of the N-sulphonyloxyquinazolines (313) does not however explain in detail the process involved in the formation of the non-aromatic intermediate (325). There are three feasible modes for the rearrangement [(313) → (325)], viz.(a) a concerted mechanism via a 6-membered cyclic transition state (cf. 327), (b) a concerted "slither" mechanism via a 4-membered cyclic transition state (cf. 328), or (c) an ion-pair mechanism (cf. 329). The involvement of radicals is thought to be unlikely. Due to the stability of the sulphonyloxy anions, it is assumed that breakage of the N-O bond of (313) is more likely to occur in a heterolytic manner forming an ion-pair (cf. 329) rather than in a homolytic manner to form radicals. A concerted mechanism via a 6-membered transition state has been invoked[215] to explain the formation of the 8-tosyloxy compound (314e) by the reaction of the N-hydroxyquinazoline (311e) with tosyl chloride. Repetition of this reaction in the presence of potassium cyanide afforded in addition to (314e) the intermediate N-tosyloxy compound (313e). Since there was no interference with the rearrangement by cyanide ion, it was proposed that the rearrangement of (313e) to yield (325e) occurred by a concerted mechanism involving a 6-membered cyclic transition state (cf. 327) rather than by an ion-pair mechanism (cf. 329). However, in the absence of isotopic labelling studies, a "slither" migration of the tosyloxy group (cf. 328) cannot be discounted. Such a "slither" migration (cf. 328) has been proposed[208] to explain the course of the reaction of isoquinoline 2-oxide (121) with tosyl chloride as mentioned in Chapter 4, part 1.

The analogous reaction of the 1-hydroxyquinolinone (330) with tosyl chloride[216] yields the N-tosyloxyquinolinone (331) which on rearrangement gives the 8-tosyloxy compound (332) presumably via



Scheme 27

an intermediate analogous to (325). Isotopic labelling studies[217] using ^{18}O-labelled tosyl chloride have been used to show that in the transition state for the rearrangement, the oxygen atoms of the tosyloxy group become equivalent. This result is consistent with an ion-pair mechanism involving a resonance-stabilised nitrenium ion (cf. 329). No 6-tosyloxy product was reported in the reactions of tosyl chloride with either the 1-hydroxyquinazoline (311e) or the 1-hydroxyquinoline (330).

The involvement of nitrenium ions as intermediates in chemical reactions has been the subject of much controversy[218-220]. Good evidence for the intermediacy of nitrenium ions can be found in reactions[221] of N-hydroxyoxindole (333) in the presence of tosyl chloride. These reactions are suggested[221] to involve an unstable N-tosyloxy compound (334) which readily rearranges to afford the 8-tosyloxy compound (335). In the presence of methanol, however, the 6-methoxyoxindole (336) is formed in addition to the expected 8-tosyloxy product (335). This result is explained by the mechanism, shown in Scheme 27, which involves nucleophilic attack by methanol on the intermediate resonance-stabilised nitrenium ion (337).

If a similar type of mechanism is operating in the rearrangement of the N-sulphonyloxyquinazolines (313 a-d), then it may be possible to intercept the intermediate nitrenium ion (cf. 329) by performing the rearrangement in the presence of other nucleophiles. With this aim in mind, the N-sulphonyloxy compound (313a) was stirred at 40° in glacial acetic acid with four molar equivalents of lithium chloride. The solid, isolated after 26 h, was shown by t.l.c. to be a mixture of the 8-tosyloxy compound (314a) and the 6-tosyloxy compound (315a) with a trace of a third slower-moving component. From its behaviour on t.l.c. and also its i.r. spectrum, this

mixture could be shown to be identical to the mixture obtained from the rearrangement of (313a) in glacial acetic acid. There was no evidence for the intervention of chloride ion in the rearrangement. Repetition of the rearrangement using four molar equivalents of sodium acetate instead of lithium chloride yielded a mixture of (314a) and (315a) with a trace of a third component, identical (i.r. spectrum and t.l.c.) to that obtained from the rearrangement of (313a) in glacial acetic acid. However, also isolated was a small quantity of a solid whose t.l.c. showed it to contain an additional component which fluoresced under ultra-violet light of wavelength 366 nm. The i.r. spectrum of this solid also showed an additional band in the carbonyl region at 1750 cm^{-1} and its ^{1}H n.m.r. spectrum contained an additional methyl absorption at τ 8.1. From this data, it appears possible that a very small proportion of the product shows incorporation of acetate ion. However, stronger evidence than this is required before any postulate concerning the mechanism of the rearrangement can be made.

The rearrangement of (313a) was also performed in the presence of pyrrolidine by stirring (313a) in dioxan with four molar equivalents of the base at 40° for 24 h. In addition to small quantities of red multi-component oils this reaction gave a brown solid whose t.l.c. showed it to be a mixture comprising mainly (314a) and (315a) with traces of at least four other components. The presence of pyrrolidine has obviously modified the nature of the products of the rearrangement but without further evidence, it is impossible to tell whether the involvement of pyrrolidine occurs during or after the rearrangement.

Sodium methanesulphonate was also investigated as a competing nucleophile in the rearrangement of (313a) because if trapping of the proposed intermediate nitrenium ion (cf. 329) did occur then the likely products would be the 8-methanesulphonyloxy compound

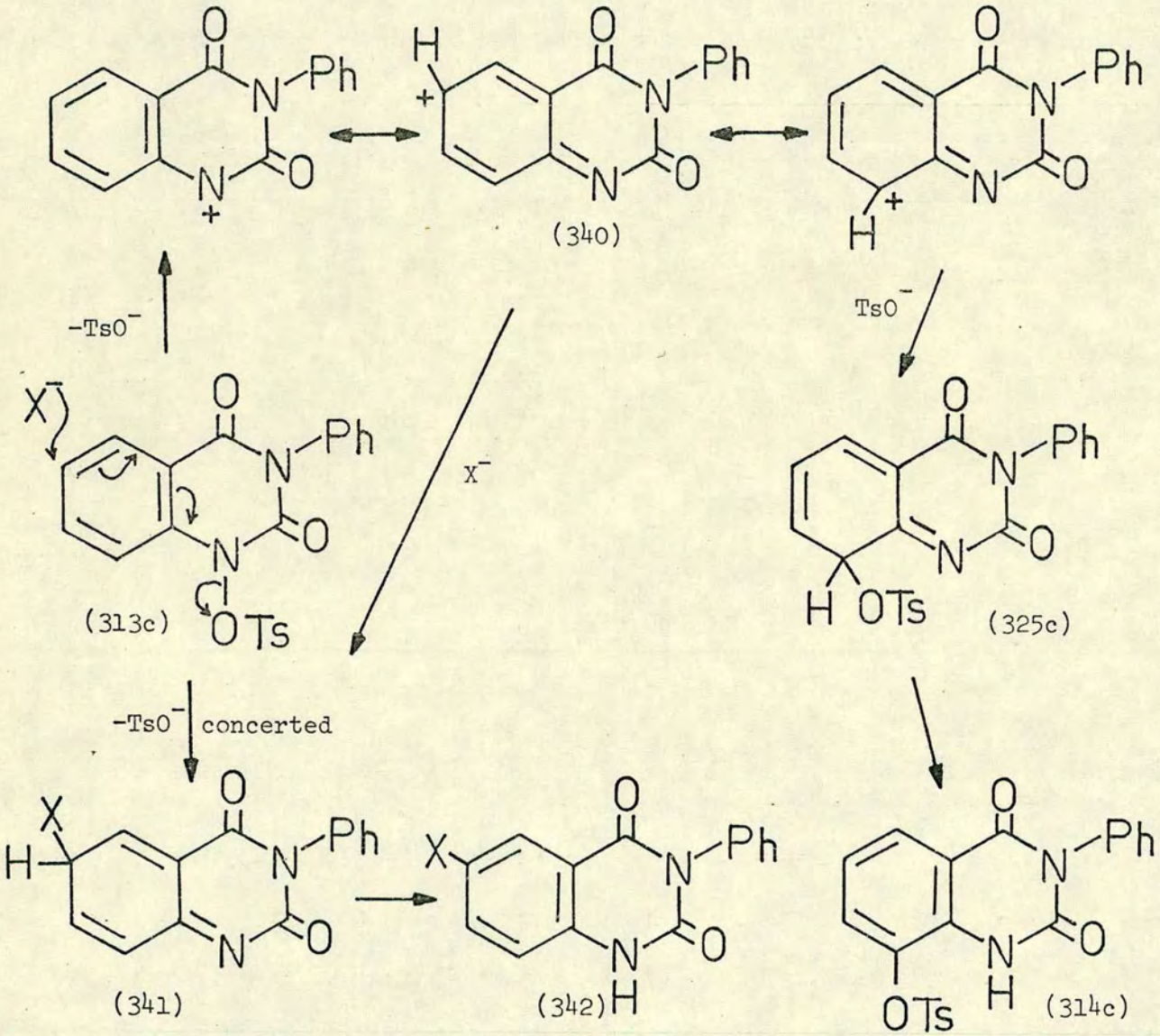
(314d) and the 6-methanesulphonyloxy compound (315d) which had already been prepared as described previously. Since 70% v/v dimethylformamide-water was required as solvent to dissolve the sodium methanesulphonate, it was necessary to perform a control experiment by rearranging (313a) in this solvent mixture by stirring at 40° for 24 h. The solid isolated from this reaction was shown by t.l.c. to be a mixture comprising (314a), (315a) and a third component identical with the mixture isolated in the thermal rearrangement of (313a) in glacial acetic acid. The rearrangement of (313a) was then carried out under the identical conditions but in the presence of four molar equivalents of sodium methanesulphonate. The solid isolated from this reaction was shown by t.l.c. and i.r. and ^{1}H n.m.r. spectra to be identical to the mixture isolated in the control experiment. There was no evidence in the ^{1}H n.m.r. spectrum of the latter mixture for the presence of either the 8-methanesulphonyloxy compound (314d) or the 6-methanesulphonyloxy compound (315d). Since there is apparently no interference in the rearrangement of (313a) by either chloride ion, pyrrolidine or methanesulphonate ion, it would appear that the mechanism for the formation of (325a) from (313a) is either concerted, i.e. *via* the transition states (327) or (325), or it occurs *via* a tight ion-pair (329) where ion-pair return takes place rapidly, preventing any competition by foreign nucleophiles. However, it is difficult to reconcile the formation of the 6-tosyloxy products (315 a-d) with a tight ion-pair mechanism since the site of attack of the anion is relatively far away from the ring nitrogen atom. The isolation, in the rearrangement of (313a) in the presence of acetate ion, of a small amount of solid whose spectral properties suggested it to contain an acetoxy group, is tentative evidence for the involvement of the ion-pair mechanism (329).

Stronger evidence for the ion-pair mechanism (329) was obtained from the reaction at room temperature of the N-hydroxyquinazoline (311c) with tosyl chloride using pyridine as solvent. The reaction mixture gave in low yield an insoluble salt which on basification gave a yellow solid, whose ^{1}H n.m.r. spectrum showed only aromatic protons. Multiplets at τ 0.86-1.02 and τ 1.10-1.41 are relatively far downfield for aromatic protons, suggesting that the protons are attached to a very electron deficient ring (e.g. the aromatic protons in a pyridinium salt). The ^{1}H n.m.r. spectrum and the ability of the yellow solid to form a water-soluble colourless salt on treatment with acid are consistent with its formulation as the betaine structure (338). This formulation is apparently confirmed by high resolution mass spectral analysis of the parent ion peak (M^+ 316) in the mass spectrum, which indicated the molecular formula $C_{19}H_{14}N_3O_2$, consistent with the cation obtained by protonation of the betaine (338). However, elemental analysis indicated the molecular formula $C_{19}H_{15}N_3O_5$ rather than $C_{19}H_{13}N_3O_2$ which corresponds to the structure (338). The elemental analyses of similar pyridinium betaines or salts (cf. Chapter 4, Parts 1 and 3) have also proved troublesome, a feature which may be in some way connected with the apparent ability of these compounds to retain water.

Further work up of the reaction mixture from the reaction of (311c) with tosyl chloride in pyridine produced a moderate yield of the 8-tosyloxyquinazoline (314c), identical to a sample obtained from the rearrangement of (313c), described previously. In addition, a colourless acidic solid was isolated whose t.l.c. showed only one spot. Its mass spectrum showed peaks at m/e 274 and 272 displaying the isotopic pattern of a molecule containing one chlorine atom. This molecular weight is consistent with the 6-chloroquinazoline structure (339b). However, the base peak in the mass spectrum appeared at m/e 238, corresponding to the

molecular ion of the compound (339a) which could not be formed by fragmentation of (339b) in the mass spectrometer. The elemental analysis of this solid also suggested that it was a mixture of the quinazolines (339a) and (339b). The quinazolinedione (339b) was prepared in high yield by the sodium dithionite reduction of the corresponding N-hydroxy compound (311d). The elemental analysis and mass and i.r. spectra of the synthetic sample were consistent with the structure (339b). The ^{1}H n.m.r. spectrum of (339b) showed a total of eight aromatic protons. A meta-coupled doublet (J 2 Hz) at τ 2.17 is assigned to H-5 and a double doublet centred at τ 2.29 showing meta-coupling (J 2 Hz) and ortho-coupling (J 8 Hz) is assigned to H-7. The ^{1}H n.m.r. spectrum of an authentic sample of the quinazolinedione (339a) showed a double doublet centred at τ 2.07, showing meta-coupling (J 2 Hz) and ortho-coupling (J 8 Hz), attributable to H-5. Examination of the ^{1}H n.m.r. spectrum of the mixture isolated from the reaction of (311c) with tosyl chloride in pyridine showed a double doublet (J 2 Hz and 8 Hz) centred at τ 2.08, integrating for 4 units, and a doublet (J 2 Hz) centred at τ 2.17, integrating for 1 unit, in addition to multiplet signals due to the other aromatic protons. Comparison of this ^{1}H n.m.r. spectrum with the ^{1}H n.m.r. spectra of the authentic samples of (339a) and (339b) suggested that the solid mixture comprised (339a) and (339b) in the ratio 4:1. This was confirmed by comparison of the ^{1}H n.m.r. spectrum of the mixture with the ^{1}H n.m.r. spectrum of an authentic mixture of (339a) and (339b) in the approximate ratio 4:1.

The solid mixture of (339a) and (339b) was methylated using dimethyl sulphate and aqueous sodium hydroxide in the hope that the mixture of the resulting N-methyl compounds (339c) and



Scheme 28

(339d) would be amenable to chromatographic separation. However, t.l.c. in a variety of solvents failed to separate the components of the methylated mixture. Authentic samples of (339c) and (339d) were obtained by the methylation (using dimethyl sulphate and aqueous sodium hydroxide) of (339a) and (339b), respectively. The respective elemental analyses and mass, i.r. and ^{1}H n.m.r. spectra confirmed the structural assignments (339c) and (339d) for the methylation products. Comparison of the ^{1}H n.m.r. spectrum of the methylated mixture with the ^{1}H n.m.r. spectra of the authentic samples of (339c) and (339d) and of an authentic mixture of (339c) and (339d) confirmed that the methylated mixture comprised (339c) and (339d) in the ratio 4:1. Attempts to separate the methylated mixture by crystallisation and sublimation were unsuccessful.

The formation of the betaine (338) and the 6-chloroquinazoline (339b) in the reaction of (311c) with tosyl chloride in pyridine can be explained as shown in Scheme 28. The first step is presumably formation of the N-tosyloxy compound (313c). Nucleophilic attack by pyridine at the 6-position of (313c) with simultaneous loss of the tosylate ion could yield the intermediate (341; X = 1-pyridyl) which would rapidly tautomerise to give the pyridinium salt (342; X = 1-pyridyl). Similar nucleophilic attack by chloride ion would yield the 6-chloro compound [(339b) or (342; X = Cl)]. Alternatively, heterolytic cleavage of the N-O bond in (313c) could yield the resonance-stabilised nitrenium ion (340). Nucleophilic attack at the 6-position would give the intermediate (341) and hence the products (342) as described before. Nucleophilic attack at C-8 on the nitrenium ion (340) by tosylate ion (i.e. ion-pair return) would explain the isolation of (314c). However, (314c) could also be formed *via* a concerted rearrangement [*cf.* (327) or (328)], as mentioned previously. The isolation of the quinazoline (339a) is somewhat

more difficult to explain. Obviously some form of reduction has occurred, either directly on the starting N-hydroxy compound (311c) or on one of the intermediates involved in the decomposition of the N-tosyloxyquinazoline (313c). However it is not obvious which species in the reaction mixture is capable of acting as a reducing agent. One possible explanation is that in addition to heterolytic fission of the N-O bond in (313c), there is some homolytic fission to give the radical pair (343). Hydrogen abstraction by the quinazolinyl radical (cf. 343) would then afford (339a). Alternatively, the formation of (339a) may be explained in terms of a nitrenium ion intermediate (cf. 340). Heterolytic fission of the N-O bond of (313c) would afford the singlet nitrenium ion in which one of the non-bonding sp^3-hybridised orbitals is empty and the other filled. Spin inversion of one of the non-bonding electrons would give the triplet nitrenium ion which would exhibit some degree of diradical character. Hydrogen abstraction and electron capture could then yield (339a). However, without any further evidence, these can only be tentative suggestions.

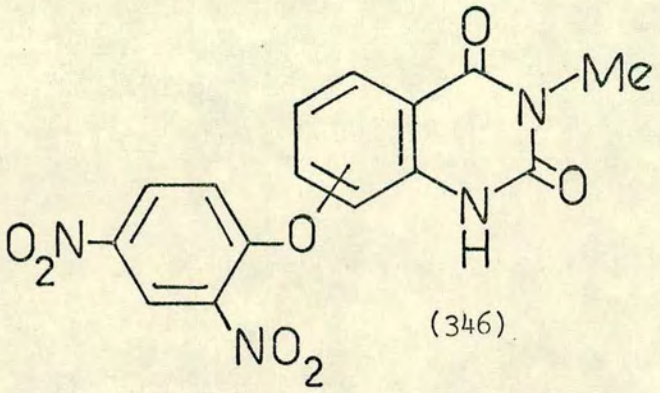
To summarise the mechanistic evidence for the rearrangement of the N-sulphonyloxy compounds (313 a-d), the involvement of the competing nucleophiles, pyridine and chloride ion, in the reaction of (311c) with tosyl chloride and pyridine can be explained in terms of a resonance-stabilised nitrenium ion (340), in which case it seems likely that the thermal rearrangement of (313 a-d) involves an ion-pair mechanism (329) with the products (314 a-d) and (315 a-d) being formed by rapid ion-pair return which makes competition by other nucleophiles difficult. However, a concerted rearrangement of (313 a-d) via either of the transition states [(327) or (328)]

cannot be discounted since the involvement of pyridine and chloride ion in the reaction of (311c) with tosyl chloride in pyridine can also be explained in terms of a concerted reaction where nucleophilic attack and loss of the tosylate anion occur simultaneously (cf. Scheme 28). The nature of the rearrangement could be completely resolved by carrying out isotopic labelling studies using ^{18}O-labelled tosyl chloride. If, on examination of the products, complete scrambling of the oxygen atoms of the tosyloxy group has occurred, then an ion-pair mechanism (329) must have been operative. If, on the other hand, the ether oxygen atom of the products (314) and (315) contains no labelled oxygen, a concerted "slither" migration of the tosyloxy group (328) would be indicated whereas if the ether oxygen atom contains only labelled oxygen, then a concerted rearrangement via a 6-membered cyclic transition state (327) would be indicated.

Having investigated the rearrangement of N-sulphonyloxy-quinazolines, it was of interest to study the similar reaction of the N-(3,5-dinitrobenzoyloxy)quinazoline (344). It was hoped that the 3,5-dinitrobenzoyloxy group would be a good enough leaving group to cause heterolytic cleavage of the N-O bond of (344) to form a nitrenium ion similar to (340). The ester (344) was prepared in quantitative yield by the reaction of the N-hydroxy compound (311a) with 3,5-dinitrobenzoyl chloride in pyridine. The elemental analysis and mass spectrum of the product were consistent with the structure (344). Also, its i.r. spectrum showed a high carbonyl absorption at 1785 cm^{-1}, characteristic of an N-acyloxy group. Its ^1H n.m.r. spectrum was also consistent with the structure (344) which was confirmed when, on heating in glacial acetic acid, the ester (344) gave, in addition to unreacted starting material (344), a quantitative yield (based on unrecovered

starting material) of the N-hydroxy compound (311a). The attempted thermal rearrangement of the ester (344) under the conditions used for the rearrangements of the tosylates (313 a-d), however, gave only an unresolvable multi-component mixture.

An attempt was also made to synthesise the N-(2,4,6-trinitrophenoxy)quinazoline (345b) by reacting (311a) with picryl chloride in dioxan at room temperature in the presence of triethylamine. However, only unresolvable multi-component mixtures were obtained possibly because the 2,4,6-trinitrophenoxy ion is such a good leaving group that the compound (345b) decomposes as soon as it is formed. Consequently, an attempt was made to synthesise the less reactive N-(2,4-dinitrophenoxy)quinazoline (345a) by the same reaction as above but using 2,4-dinitrochlorobenzene instead of picryl chloride. Work up of the reaction mixture gave in addition to starting material (311a) an orange oil in extremely high yield. This oil was shown by t.l.c. to contain 2,4-dinitrochlorobenzene and two other yellow components. The high weight of the oil suggested the presence of solvent or of products derived from the solvent. On attempting to evaporate the oil under reduced pressure (oil pump) and with heating, the components of the oil were seen to have decomposed since t.l.c. of the resultant oil showed it to be a mixture of at least five components. In another attempt to synthesise the compound (345a), the N-hydroxyquinazoline (311a) was reacted under reflux with 2,4-dinitrochlorobenzene in the presence of ethanolic sodium ethoxide. This reaction gave mainly multi-component mixtures but, in addition, two acidic solids were isolated. One was identified by comparison with an authentic sample as 2,4-dinitrophenol. The other acidic product was shown by its elemental analysis and mass spectrum to have the molecular formula $C_{15}H_{14}N_4O_7$. Its i.r. spectrum contained a band at 3,200 cm^{-1}



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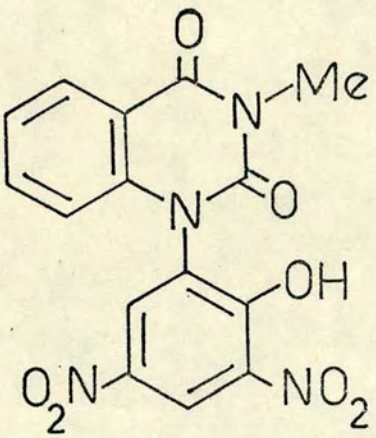

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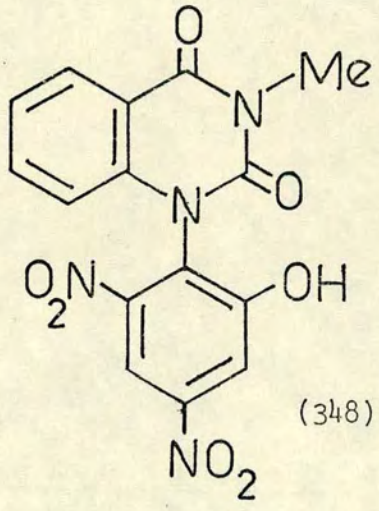

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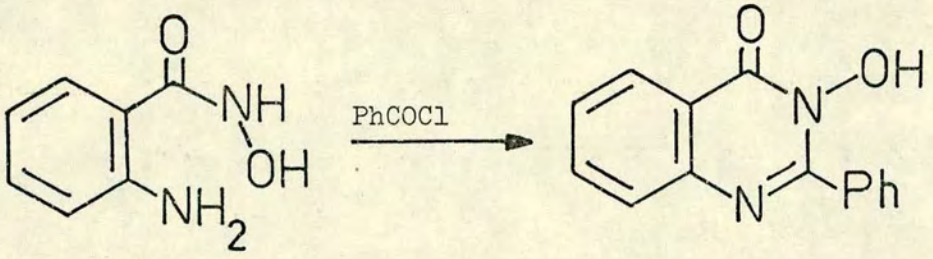

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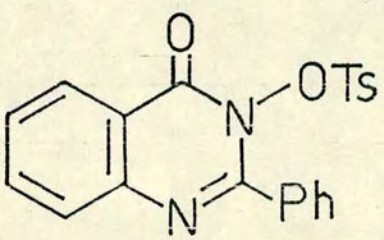
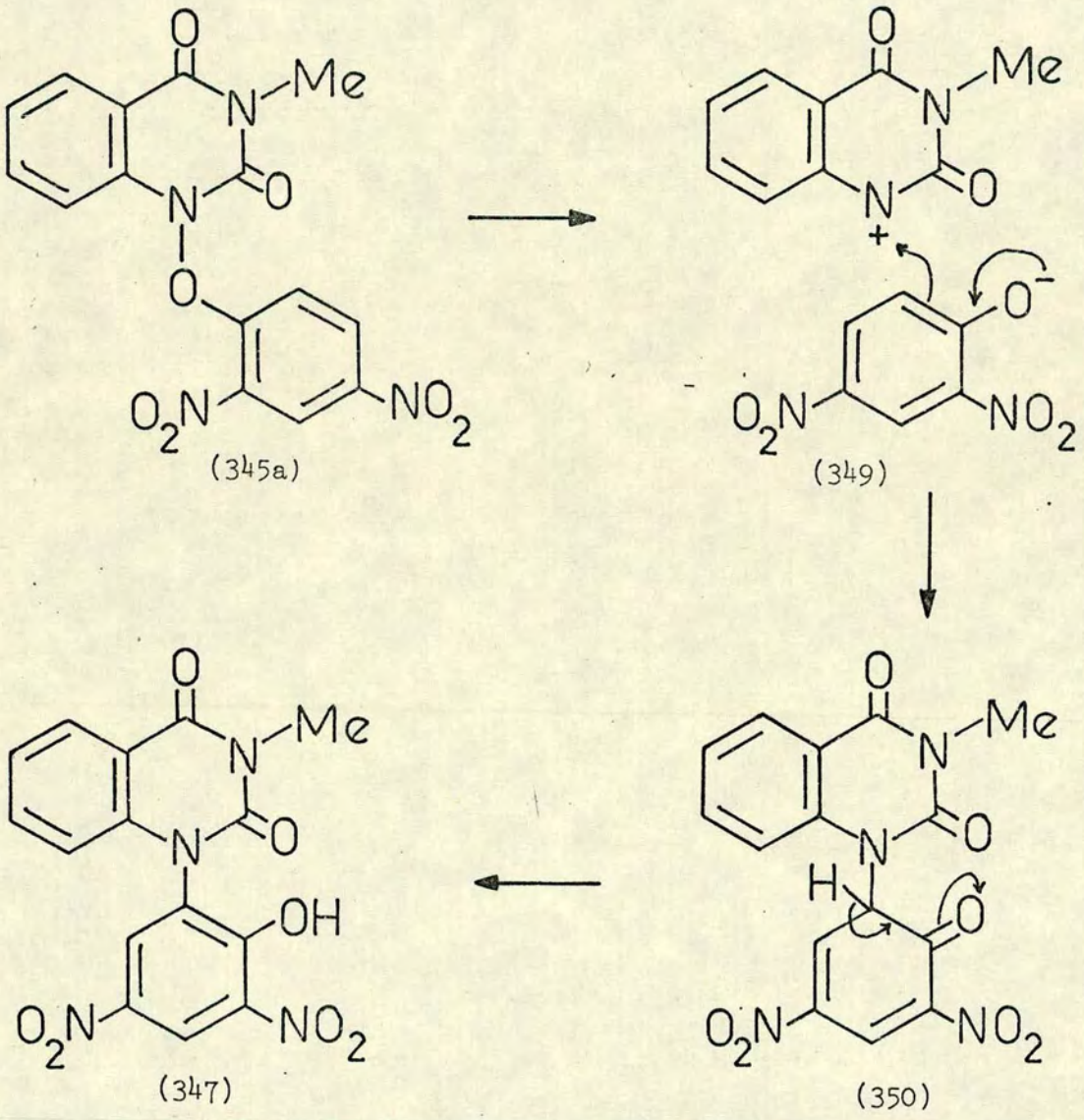
(352)



(353)

attributable to NH or OH absorption and three bands in the carbonyl region (1715, 1680 and 1665 cm^{-1}) as well as absorption at (1560, 1540, 1355 and 1330 cm^{-1}) due to two nitro groups. The unknown acidic solid also gave no deep colour in the presence of iron (III) chloride. This evidence is consistent with a 6- or 8-aryloxyquinazoline (346) which might be formed by rearrangement of the N-aryloxy compound (345a). However, the ^1H n.m.r. spectrum of the compound does not fit this postulate since it shows two one-proton doublets at τ 1.13 and 1.40 corresponding to meta-coupled protons (J_{meta} 3 Hz). The identical coupling constants suggest that the two protons are coupled to each other and to no other protons in the molecule, a fact which was confirmed by decoupling the signals. Irradiation at 2739 Hz caused the doublet at τ 1.40 to collapse to a singlet, while irradiation at 2713 Hz caused the doublet at τ 1.13 to collapse to a singlet. In both cases, there was no other effect on the spectrum. Since these two protons are so far downfield, it is assumed that they are the protons adjacent to the nitro groups. Therefore, the benzene ring carrying the two nitro groups must be 1,2,3,5-tetrasubstituted. Consequently, the reaction must have involved more than just simple displacement of chloride ion from the 2,4-dinitrochlorobenzene. The other four aromatic signals in the ^1H n.m.r. spectrum are therefore assigned to the quinazoline nucleus showing that no substitution has taken place in the fused benzene ring. The signal at lowest field is assigned to H-5 and appears as a double doublet at τ 1.90 (ortho-coupled to H-6 and meta-coupled to H-7). The signal assigned to H-6 appears as a triplet at τ 2.70 due to ortho-coupling with H-5 and H-7. The meta-coupling to H-8 is too small to be observed and indeed H-8 appears as only an ortho-coupled doublet at τ 3.30. The remaining signal assigned to H-7 appears as a double triplet at


O
N
Me
O
N
O
O2N
NO2
(345a)
O
N
Me
O
N
+
O−
O2N
NO2
(349)
O
N
Me
O
N
H
O
O2N
NO2
(350)
O
N
Me
O
N
OH
O2N
NO2
(347)

Scheme 29

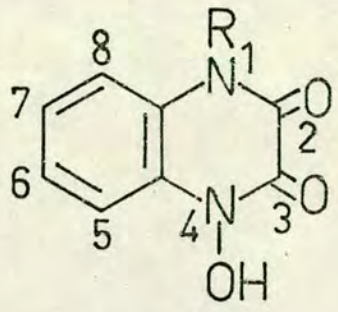
τ 2.41 (ortho-coupled to H-6 and H-8 and meta-coupled to H-5). This aromatic splitting pattern confirms that no substitution has taken place in the fused benzene ring. Two possible structures which fit all of the spectral data are (347) and (348) which, however, are both phenols and would be expected to give a colour in the presence of iron (III) chloride. The mode of formation of (348) is difficult to rationalise but the formation of (347) could possibly be explained by an ion-pair mechanism (Scheme 29) which involves initial formation of the N-aryloxy compound (345a). Heterolytic cleavage of the N-O bond of (345a) would afford the ion-pair (349). Electrophilic attack by the nitrenium ion on the 2,4-dinitrophenolate anion, as shown, would yield (350) which would readily rearrange to give the product (347). This postulate is supported by the isolation of 2,4-dinitrophenol from the reaction of (311a) with 2,4-dinitrochlorobenzene. This strongly suggests that the N-aryloxyquinazoline (345a) has in fact been formed and has decomposed under the reaction conditions to give the nitrenium ion and the 2,4-dinitrophenolate anion (cf. 349) which would yield the phenol on acidification. However, it is obvious that more work is necessary before any definitive statement concerning the mechanism of the reaction of (311a) with 2,4-dinitrochlorobenzene can be made.

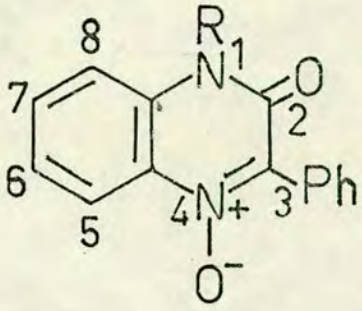
As an extension of the studies with the compounds (311) the reaction of the 3-hydroxyquinazoline (352) with tosylchloride in pyridine was also investigated. Rearrangement of the 3-tosyloxy compound (353) is unlikely to be concerted for structural reasons. Consequently, if rearrangement of (353) were to occur, then the likely mechanism would be an ion-pair mechanism. The N-hydroxyquinazoline (352) was prepared[222] in good yield by the cyclisation of 2-aminobenzohydroxamic acid (351)[223] with benzoyl chloride. The reaction of the N-hydroxy compound (352) with tosyl chloride in

pyridine yielded, in addition to a small quantity of the starting material (352), an almost quantitative yield (based on unrecovered starting material) of the 3-tosyloxyquinazoline (353).

The elemental analysis and mass spectrum of the product were consistent with the molecular formula $C_{21}H_{16}H_2O_4S$ and the structure (353) was confirmed by hydrolysis using aqueous sodium hydroxide to give an almost quantitative yield of the N-hydroxy compound (352). The attempted rearrangement of (353) was carried out as for the rearrangements of (313 a-d) in a cold-finger vacuum sublimation apparatus at the melting point of (353) (170°). However, t.l.c. of the cooled melt showed it to be a mixture consisting mainly of the starting material (353) and at least four minor components. Since the rearrangement appeared to be so sluggish and since a number of products were formed, the reaction was not investigated further.

Part 3. 1-Hydroxyquinoxaline-2(1H),3(4H)-diones and 3-Phenylquinoxalin-2(1H)-one 4-Oxides





As mentioned previously (Chapter 4, Part 2, p.117), it was of interest to investigate the reactivity of N-hydroxyquinoxalinediones towards acylating agents to find out if the derived N-acyloxy compounds were susceptible to nucleophilic attack in a similar manner to their 5-membered ring analogues, N-acyloxybenzimidazolones [Part 2; (305) → (306; X=OAc)][191].

With this objective in mind, a series of N-hydroxyquinoxalinediones (357a-c) was prepared by the base-catalysed cyclisation of the anilides (355a-c) which were readily available from the condensation of the 2-nitroanilines (354a-c) with cyanoacetyl chloride. The N-benzylanilines (354c-e) were obtained in good yields from the reactions[224] of benzylamine with the appropriate 2-chloronitrobenzenes. The anilides (355b)[225,226] and (355c)[226] were obtained in high yields from the condensation of (354b) and (354c), respectively, with cyanoacetyl chloride. The condensation of cyanoacetyl chloride with the chloro compound (354d) gave a high yield of the corresponding anilide (355d) whose structure was confirmed by its elemental analysis and its mass, i.r. and ^{1}H n.m.r. spectra. The i.r. spectrum showed cyano (2250 cm^{-1}), carbonyl (1680 cm^{-1}) and nitro group (1530 and 1350 cm^{-1}) absorption. The ^{1}H n.m.r. spectrum showed, in addition to the eight aromatic protons, a doublet (J 14 Hz) centred at τ5.05, a doublet (J 14 Hz) centred at τ5.39, each corresponding to one proton, and a singlet at τ6.58 due to two protons. It seems that

restricted rotation about the N-benzyl C-N bond has rendered the benzylic protons non-equivalent. Geminal coupling (J 14 Hz) between the two benzylic protons explains the appearance in the spectrum of the two one-proton doublets. The singlet at τ6.58 can therefore be assigned to the methylene group of the N-cyanoacetyl substituent. The ^{1}H n.m.r. spectrum of the 5-methyl-2-nitroanilide (355e), which was obtained in high yield from the condensation of (354e) with cyanoacetyl chloride, shows a similar pattern. The benzylic protons are again non-equivalent due to restricted rotation and appear as two doublets showing geminal coupling (J 14 Hz) centred at τ5.03 and τ5.42. In addition, the signal due to the methylene group of the N-cyanoacetyl substituent is also split, showing non-equivalence of the methylene protons, and appears as two close singlets at τ6.68 and τ6.71 respectively. Thus, there must also be restricted rotation about the C-C=O bond of the cyanoacetyl group in (355e). The remainder of the ^{1}H n.m.r. spectrum is consistent with the structure (355e) which is further confirmed by the elemental analysis and mass and i.r. spectra of the compound.

Cyclisation of the anilides (355b) and (355c) using 20% w/v aqueous potassium hydroxide gave high yields of the known N-hydroxyquinoxalinediones (357b)[225,226] and (357c)[226]. The similar cyclisation of (355d) gave a high yield of the 7-chloro-4-hydroxyquinoxaline (357d). The i.r. spectrum of this product showed no nitro group absorption but contained a broad band at 3200-2500 cm^{-1}, characteristic of an N-hydroxyquinoxaline (357d), and it also gave a deep purple colour in the presence of iron (III) chloride, as did the compounds (357 a-c), characteristic of N-hydroxy derivatives. The structure of the product (357d) was confirmed by its elemental analysis and its mass and ^{1}H n.m.r. spectra. Cyclisation of the anilide (355e) using aqueous potassium hydroxide gave a good yield of the 7-methyl compound (357_e) which gave a deep purple colour in the presence

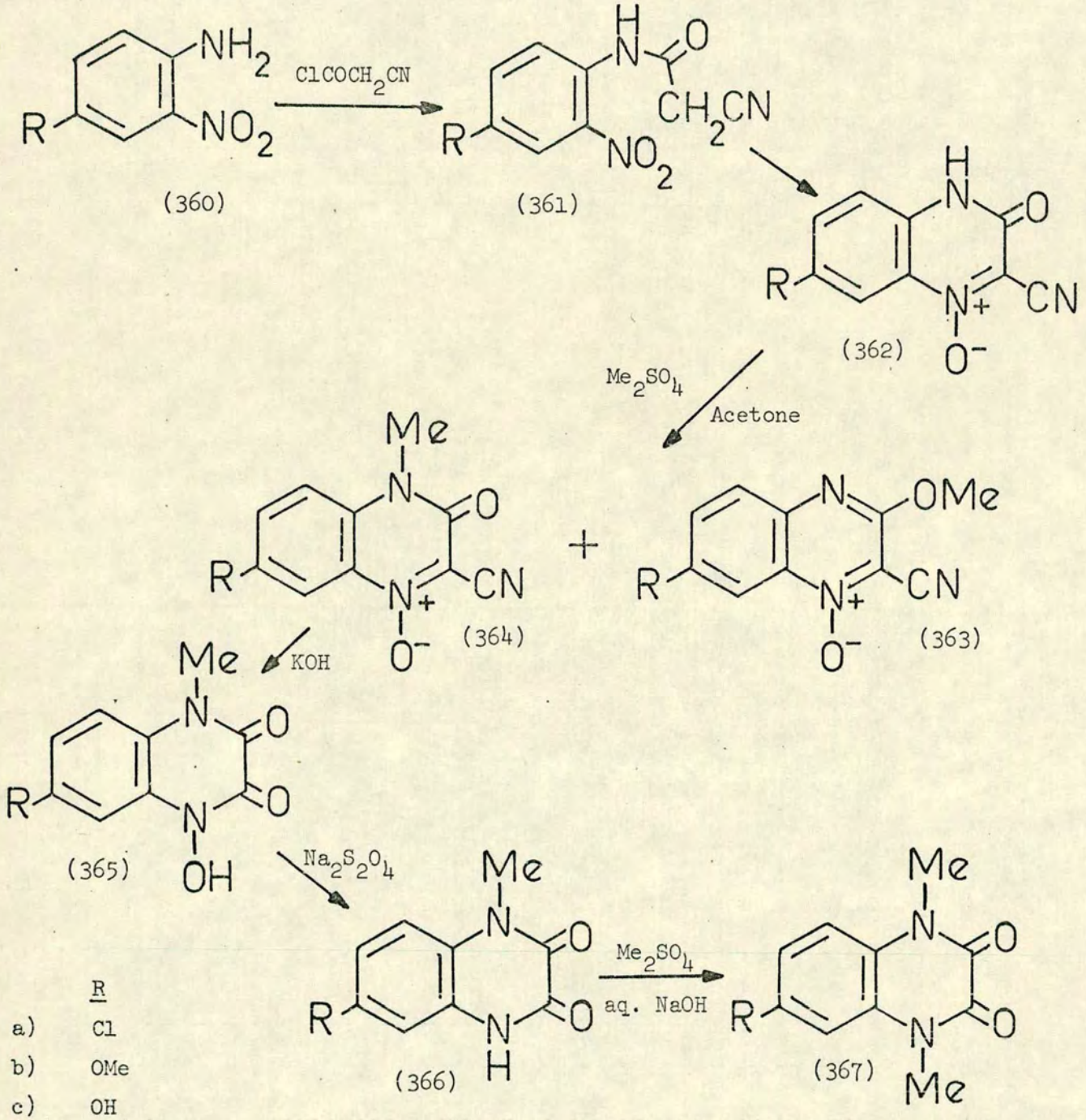
of iron (III) chloride and showed broad OH absorption at 3150 cm^{-1} in its i.r. spectrum, features characteristic of a cyclic N-hydroxy compound. The elemental analysis and mass and ^{1}H n.m.r. spectra were also consistent with the structural assignment (357e). In addition to the known[227] N-hydroxycompound (357a) which was obtained in moderate yield, the cyclisation of the anilide (355a)[226,228] gave a solid whose mass spectrum showed it to be a mixture of the N-hydroxy compound (357a) and quinoxaline-2(1H),3(4H)-dione (357a; H for OH)[229]. The N-hydroxy compound (357a) was also prepared in high yield by the hydrolytic removal of the cyano group from the 3-cyanoquinoxaline 4-oxide (356a)[226,228] using sodium ethoxide as catalyst.

It has been shown[225] that acetylation of the N-hydroxy compound (357b) with acetic anhydride under relatively mild conditions affords the N-acetoxy derivative (358a). It was hoped that more prolonged treatment with acetic anhydride might induce a rearrangement analogous to that observed in the N-hydroxybenzimidazolone series [Part 2; (305) → (306; X=OAc)]. However, heating (358a) in acetic anhydride at 100° for 3 h gave a quantitative recovery of the starting material. Obviously, the acetoxy group is not a sufficiently good leaving group in this case to permit the rearrangement to take place. So, an investigation of the reactions of the N-hydroxy compounds (357a-e) in the presence of tosyl chloride was undertaken.

The reaction of the N-methyl compound (357b) in dioxan in the presence of dilute aqueous sodium hydroxide with tosyl chloride gave, in addition to a brown intractable gum, a moderate recovery of the starting material (357b). No other identifiable material could be isolated. On the other hand, heating (357b) under reflux in dimethylformamide in the presence of tosyl chloride gave, in addition to an unresolvable multi-component mixture, a moderate yield of a pale coloured solid whose t.l.c. showed it to be a

two component mixture containing no starting material. The mass spectrum of the mixture showed peaks at m/e 212 and 210, consistent with a chlorine-containing compound of formula, $C_9H_7ClN_2O_2$, and at m/e 192 (which is unlikely to be formed by fragmentation of the chlorine-containing compound) consistent with a compound of formula, $C_9H_8N_2O_3$. The mixture was separated by two methods. Washing the solid with warm 2N aqueous sodium carbonate gave a moderate yield of a colourless solid whose elemental analysis was not quite correct for $C_9H_7ClN_2O_2$. However, this formula was confirmed by an exact mass determination on the molecular ion peaks at m/e 212 and 210 in the mass spectrum. A possible structure, based on mechanistic arguments (see later), is 7-chloro-1-methylquinoxaline-2(1H),3(4H)-dione (359a). Acidification of the sodium carbonate washings gave a solid whose t.l.c. showed it to be a two component mixture containing more of the chlorine-containing compound. In order to make this mixture more amenable to separation by column chromatography, it was methylated using dimethyl sulphate and dilute aqueous sodium hydroxide. Dry-column chromatography over silica resulted only in a partial separation. In addition to a solid two component mixture, a moderate yield of a colourless solid of formula $C_{11}H_{12}N_2O_3$ (elemental analysis and mass spectrum) was obtained which was subsequently identified as the 6-methoxy-1,4-dimethylquinoxaline (367b). The ^1H n.m.r. spectrum showed three aromatic protons, two N-methyl groups (two three-proton singlets at τ6.42 and 6.44) and one O-methyl group (a three-proton singlet at τ6.15).

Alternatively, the solid mixture from the reaction of (357b) with tosyl chloride in dimethylformamide was separated by methylation using dimethyl sulphate and dilute aqueous sodium hydroxide. Dry-column chromatography over alumina of the methylated mixture gave a moderate yield of the methoxy compound (367b) and a low yield of



	R
a)	Cl
b)	OMe
c)	OH

Scheme 30

the chlorodimethylquinoxaline (367a). The elemental analysis and mass spectrum of the latter product were consistent with the molecular formula, $C_{10}H_9ClN_2O_2$, as was the ^1H n.m.r. spectrum which showed three aromatic protons and two N-methyl groups (two three-proton singlets at τ6.38 and 6.40).

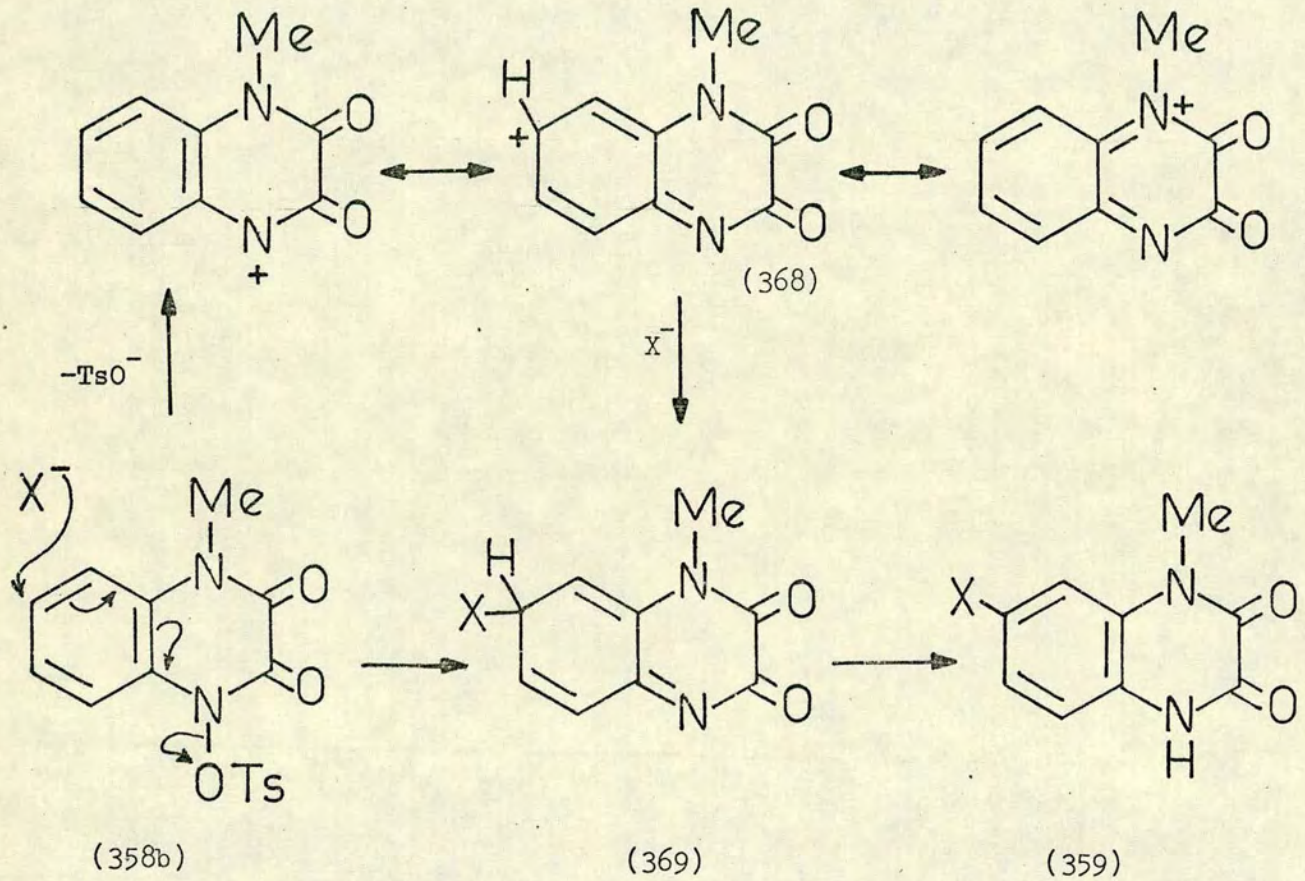
The proposed structures for the products from the reaction of (357b) with tosyl chloride in dimethylformamide and their methylated derivatives were firmly established by unambiguous synthesis as shown in Scheme 30. The known[226,228] 2-nitroanilides (361 a and b) were prepared by the condensation of the 2-nitroanilines (360 a and b), respectively, with cyanoacetyl chloride. Cyclisation of (361a) using aqueous sodium hydroxide in pyridine gave the known[226,228] N-oxide (362a) in moderate yield. The similar cyclisation of (361b), however, gave a low yield of the known[226,228] N-oxide (362b). Cyclisation of (361b) with ethanolic sodium ethoxide, to give a moderate yield of (362b), was accompanied by cleavage of the amide (361b) to 4-methoxy-2-nitroaniline (360b). Methylation of (362a) using dimethyl sulphate in anhydrous acetone gave a high yield of a two component mixture which was separated by dry-column chromatography over alumina to give as the faster-moving and minor component the O-methylated N-oxide (363a). The elemental analysis and mass spectrum of the compound were consistent with this structure. The i.r. spectrum showed no carbonyl absorption but did show a strong C-O absorption at 1150 cm^{-1}. The ^1H n.m.r. spectrum contained in addition to three aromatic protons, a three-proton singlet at τ5.69, consistent with an O-methyl group. The slower-moving and major component is assigned the N-methyl structure (364a) since the i.r. spectrum showed carbonyl absorption at 1660 cm^{-1} and the ^1H n.m.r. spectrum contained a three-proton singlet at τ6.10, consistent with an N-methyl group. The elemental analysis and mass spectrum were also in accord with this structure. Methylation of

(362b) with dimethyl sulphate in anhydrous acetone gave, in addition to a small quantity of the starting material (362b), a mixture of the two methylated isomers (363b) and (364b) which were separated by dry-column chromatography. The i.r. spectrum of (364b) showed carbonyl absorption (1640 cm^{-1}) and its ^{1}H n.m.r. spectrum contained O-methyl absorption (τ5.99) and N-methyl absorption (τ6.06) confirming the N-methylated structure (364b). The i.r. spectrum of (363b) showed no carbonyl absorption and its ^{1}H n.m.r. spectrum showed two O-methyl groups (τ5.69 and 5.96) confirming the O-methylated structure (363b).

The N-hydroxyquinoxalinediones (365 a and b) were obtained in near quantitative yield by the action of aqueous potassium hydroxide on the cyano-N-oxides (364 a and b), respectively. The analytical and spectral data for both (365 a and b) are consistent with their formulation as N-hydroxy compounds and, in addition, both give purple colours in the presence of iron (III) chloride.

Reduction of (365a) with sodium dithionite gave a high yield of the 6-chloro-1-methyl compound (366a), which was shown by elemental analysis and mass spectrum to be isomeric with the chloro compound obtained from the reaction of (357b) with tosyl chloride in dimethylformamide. However, the melting points and i.r. spectra of the two compounds show that they are different. The similar reduction of (365b) gave a high yield of the 6-methoxy-1-methyl compound (366b) whose structure was confirmed by its elemental analysis and mass spectrum.

The quinoxalinedione (366a) was methylated using dimethyl sulphate and aqueous sodium hydroxide to give, in addition to a high recovery of the starting material (366a), a low yield of the 6-chloro-1,4-dimethyl compound (367a) whose melting point, mixed melting point and i.r. spectrum showed it to be identical to the compound obtained by methylation of the product mixture from the reaction of (357b) with



X

a) Cl

b) OH

c) OTs

Scheme 31

tosyl chloride in dimethylformamide. Since the chloro compound isolated from the reaction of (357b) with tosyl chloride in dimethylformamide gives, on methylation, (367a) and since it has been shown not to be the 6-chloro derivative (366a), the product from the tosyl chloride reaction must have the 7-chloro-1-methyl structure (359a). Methylation of (366b) with dimethyl sulphate and aqueous sodium hydroxide gave, in addition to a moderate recovery of starting material (366b), a good yield of the 6-methoxy-1,4-dimethyl compound (367b) which was shown by its melting point, mixed melting point and i.r. spectrum to be identical to the compound obtained from methylation of the product mixture from the reaction of (357b) with tosyl chloride in dimethylformamide. Thus, the second of the products of the latter reaction must have the 6-hydroxy structure (366c) or the 7-hydroxy structure (359b). By analogy with the other product (359a) and on mechanistic grounds, the hydroxy compound is assigned the structure (359b).

The formation of (359a) and (359b) can be explained (Scheme 31) by initial formation of the N-tosyloxy compound (358b) which may fragment by heterolysis of the N-O bond to give the resonance stabilised nitrenium ion (368). Nucleophilic attack by chloride ion might then yield the intermediate (369a) which on prototropic rearrangement would yield the product (359a). Alternatively, the intermediate (369a) could be formed directly from the N-tosyloxy compound (358b) by nucleophilic attack by chloride ion with simultaneous loss of tosylate ion. The hydroxy compound (359b) could be formed by the same types of process involving nucleophilic attack by water present in the solvent or by hydroxide ion derived from the water. Another possible explanation for the formation of (359b) could be nucleophilic attack by tosylate ion and hydrolysis of the 7-tosyloxy compound (359c) which would thus be formed.

Two attempts were made to demonstrate competing attack by external nucleophiles in the reactions of (357b) with tosyl chloride. Thus, the reaction of (357b) with tosyl chloride in dimethylformamide was performed at -40° in the presence of triethylamine. It was hoped that the N-tosyloxy compound (358b) would be formed but that, at the low temperature, it would not decompose so that when, after 5 min., the reaction mixture was quenched with methanol and allowed to warm up, nucleophilic attack by methanol would occur yielding the methoxy compound (359d). However, the solid obtained on work up of the reaction mixture was shown by t.l.c. and its mass and i.r. spectra to be identical to the mixture of (359 a and b) obtained from the reaction of (357b) under reflux with tosyl chloride in dimethylformamide. Similarly, carrying out the reaction of (357b) in dimethylformamide with tosyl chloride in the presence of triethylamine and sodium acetate at -40° gave only a mixture of (359 a and b), identical to that isolated as described previously. There was no evidence to suggest incorporation of acetate ion into the products.

Attention was now focussed on the reactions of the N-hydroxy compounds (357a-e) in pyridine with tosyl chloride. The reaction of (357a) at room temperature with tosyl chloride in pyridine gave on work up a pale solid whose mass spectrum showed a molecular weight of 162 but also minor peaks at m/e 198 and 196 corresponding to the isotopic pattern of a chlorine-containing compound. Crystallisation of this solid gave in good yield the pure quinoxaline-2(1H),3(4H)-dione (370a), identical to an authentic sample. No more pure material could be isolated from the mother liquors or crystallisation liquors. The minor peaks at m/e 198 and 196 in the mass spectrum of the crude solid suggest the presence of the 6-chloro compound (370b) which would presumably be formed by a mechanism analogous to that shown in Scheme 31. The formation of (370a) shows that reduction of the

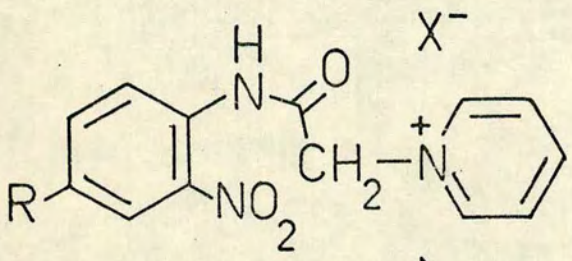
starting material has occurred. The nature of the reducing agent is not at all obvious although (357a) appears to be easily reduced since in aqueous potassium hydroxide cyclisation of (355a) to form (357a) is accompanied by some deoxygenation to give (370a).

The room temperature reaction of (357b) with tosyl chloride in pyridine takes a completely different course, an insoluble colourless salt being obtained in high yield. On dissolving in water and basifying carefully with dilute aqueous sodium hydroxide, the salt afforded a quantitative yield of the brilliant yellow betaine (371a). The mass spectrum of this product showed a molecular ion at 254 mass units, consistent with the cation (cf. 372). The ^1H n.m.r. spectrum of the yellow solid showed an N-methyl group (τ6.12) and a total of eight aromatic protons, with aromatic multiplets as far downfield as τ0.95 and 1.19 suggesting the presence of a very electron deficient ring, consistent with the pyridinium betaine structure (371a). The yellow product also readily formed a hydrochloride (372), again behaviour consistent with the betaine structure (371a). However, the elemental analysis was not consistent with the expected formula, $C_{14}H_{11}N_3O_2$, but rather $C_{14}H_{15}N_3O_5$, corresponding to the expected molecular formula plus two water molecules and an extra oxygen atom. Similarly, the elemental analysis of the hydrochloride did not correspond to the expected formula, $C_{14}H_{12}ClN_3O_2$, but instead was in accord with $C_{14}H_{14}ClN_3O_4$, equivalent to the expected molecular formula plus one molecule of water and an extra oxygen atom. However, an exact mass determination on the molecular ion peak at 254 mass units in the mass spectrum of the hydrochloride (372) indicated the molecular formula, $C_{14}H_{12}N_3O_2$, consistent with the cation (cf. 372).

Methylation of the yellow betaine (371a) in dimethylformamide with methyl iodide afforded the pyridinium iodide (373) in high yield.

The mass spectrum showed a molecular ion of 268 mass units, consistent with the cation (cf. 373) and the elemental analysis was consistent with the formula, $C_{15}H_{14}IN_3O_2$, expected for the pyridinium iodide (373). The ^1H n.m.r. spectrum showed two N-methyl groups (six-proton singlet at τ6.32) and a total of eight aromatic protons, with aromatic multiplets as low downfield as τ0.79 and 1.19, indicative of the presence of a pyridinium ring.

Because of the anomalous elemental analysis of the betaine (371a) and its hydrochloride (372), attempts were made to degrade the betaine (371a) in an effort to provide additional support for the structural assignment (371a) and also for the position of substitution in the quinoxaline nucleus. The attempted hydrolytic cleavage of the pyridine ring using sodium hydroxide was unsuccessful partly due to the insolubility of the starting material (371a) (which was recovered unchanged in high yield) but also due to the formation of intractable solids from the small amount of the betaine (371a) which did dissolve. On the other hand, heating (371a) under reflux in piperidine and methanol was more successful. Again, due to the insolubility of (371a) in the reaction medium, a 55% recovery of the starting material (371a) was obtained but on further work up a low yield of the 7-aminoquinoxaline (374a) was isolated. The structure (374a) was confirmed by its elemental analysis and mass spectrum and also by its i.r. spectrum which showed NH absorption (3350, 3250 and 1620 cm^{-1}) and OH absorption (3100-2500 cm^{-1}), in addition to carbonyl absorption (1690 and 1650 cm^{-1}). The analytical and spectral data, however, do not discount the 6-amino structure (366; R=NH_2). Heating the pyridinium iodide (373) under reflux with piperidine in methanol gave a high yield of the 6-amino-1,4-dimethylquinoxaline (374b), whose structure was confirmed by its elemental analysis and mass spectrum. Its i.r. spectrum contained



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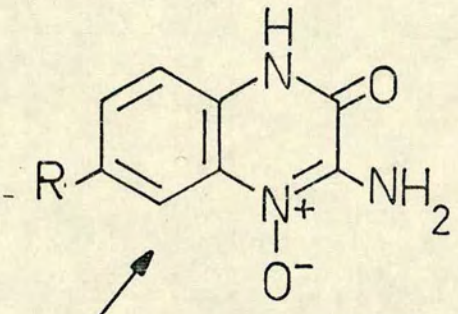

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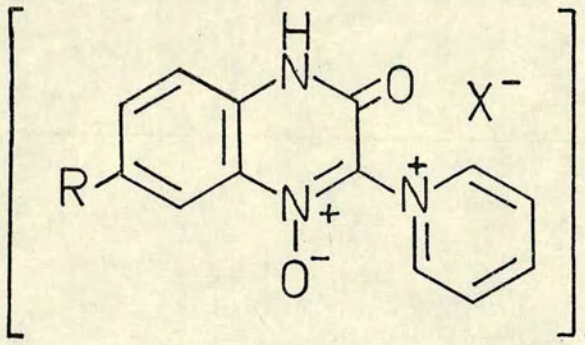


(376)

carbonyl absorption (1680 and 1660 cm^{-1}) and NH absorption (3450, 3350 and 3200 cm^{-1}) and its ^{1}H n.m.r. spectrum showed two N-methyl groups (six-proton singlet at τ6.63) and a primary amino group (two-proton singlet at τ4.81) and three aromatic protons, H-8 appearing as a doublet (J_{ortho} 8 Hz) centred at τ2.93. The structure of the amine (374b) was confirmed by its conversion into the chloro compound (367a) [synthesised previously (Scheme 30)] by the Sandmeyer reaction which involved treating the diazonium salt derived from (374b) with an aqueous solution of copper (I) chloride.

Precedent for the cleavage of pyridinium salts to primary amines using piperidine and methanol is found in the synthesis[173,174,226] of the 3-aminoquinoxaline 4-oxides (377) by base-catalysed cyclisation of the pyridinium salts (375) using piperidine as catalyst. Presumably, the intermediate pyridinium salts (376) are formed by an aldol-type condensation of the nitro group of (375) with the ortho- side chain. Cleavage of the pyridine ring in (376) by piperidine then affords the 3-amino 4-oxides (377).

Thus, formation of the amine (374b) from (373) by the action of piperidine and methanol provides good support for the structural assignment (373), which in turn provides further evidence for the betaine structure (371a) proposed for the product of the reaction of (357a) with tosyl chloride in pyridine. The structure (371a) is further supported by the formation of the amino compound (374a) on treatment of (371a) with piperidine in methanol but there is no evidence to distinguish between substitution of the quinoxaline ring at the 6- or 7-position. The betaine product (371a) is presumably formed by nucleophilic attack of pyridine on the N-tosyloxy intermediate (358b) by a mechanism identical to that shown in Scheme 31. Thus, all of the evidence, both chemical and spectral, with the exception of the elemental analysis of (371a)

and its hydrochloride (372), are consistent with the 1-(quinoxalin-7 -yl)pyridinium betaine structure (371a) for the product of the reaction of (357b) with tosyl chloride in pyridine.

In a similar manner, treatment of the N-benzyl compound (357c) in pyridine with tosyl chloride gave an almost quantitative yield of a colourless salt which was dissolved in water and basified to give a yellow solid, formulated by analogy with (371a) as the betaine (371b). The mass spectrum of this product lacked a peak due to the parent ion and its elemental analysis did not correspond to the molecular formula, $C_{20}H_{15}N_3O_2$, required for (371b) but instead indicated the formula, $C_{20}H_{17}N_3O_4$, corresponding to the expected molecular formula plus one molecule of water and one extra oxygen atom. The anomalous analytical data of (371b) are thus very similar to those of (371a). Stronger evidence for the betaine structure (371b) for the product of the reaction of the N-hydroxy compound (357c) with tosyl chloride in pyridine is its conversion, in low yield, by heating with piperidine in methanol into the primary amine (374c). In accord with this structure, the i.r. spectrum of (374c) contained absorption bands due to a primary amino group (3450, 3350 and 3200 cm^{-1}), broad absorption at 3100-2500 cm^{-1}, characteristic of the NH absorption of a cyclic lactam, and carbonyl absorption (1700 and 1680 cm^{-1}). The structure of the amine (374c) was further confirmed by its elemental analysis and mass spectrum.

If, in the reaction of (357c) with tosyl chloride in pyridine, nucleophilic attack by pyridine occurs at the 7-position in the quinoxaline nucleus, then the product will have the 1-(quinoxalin-7-yl)pyridinium betaine structure (371b) and hence the product from the piperidine-methanol reaction will have the 7-amino structure (374c). The Sandmeyer reaction of this amine (374c) should yield the 7-chloro compound (378) which in turn should be identical with the product of the sodium dithionite reduction of the N-hydroxy

compound (357d). If the products from the Sandmeyer reaction of the amino product (374c) and from the dithionite reduction of (357d) are identical, then the position of substitution in the quinoxaline nucleus would be unambiguously ascertained as the 7-position.
As mentioned previously (p.150), cleavage of the pyridinium iodide (373) using piperidine-methanol to give the primary amine (374b), followed by Sandmeyer reaction to give the chloro compound (367a), demonstrated that in the formation of the betaine (371a) nucleophilic attack had occurred at either C-6 or C-7 in the quinoxaline nucleus. Thus, if the product obtained from the Sandmeyer reaction of the amine formed from the betaine (371b) is different from the dithionite reduction product, then the position of substitution in the quinoxaline nucleus of (371b) must then be the 6-position. In practice, the chloro compound (378) was obtained in almost quantitative yield by dithionite reduction of (357d) and its structure was confirmed by its elemental analysis and mass and i.r. spectra. However, the attempted Sandmeyer reaction of (374c) gave a brown solid whose i.r. spectrum showed only one carbonyl absorption (1670 cm^{-1}) and an absorption band at 2200 cm^{-1} which suggested the presence of a diazonium group. The attempted crystallisation of this solid yielded a brown intractable solid whose i.r. spectrum lacked any absorption around 2200 cm^{-1}. However, this product could not be characterised due to its extreme insolubility. Also isolated from this reaction was a second brown solid whose i.r. spectrum showed only a weak absorption at 2200 cm^{-1}. This product decomposed on attempted crystallisation. In the absence of any definitive result from the attempted Sandmeyer reaction of the amine (374b), the betaine product from the reaction of the N-hydroxy compound (357c) with tosyl chloride in pyridine is assigned the quinoxalin-7-yl

structure (371b) on mechanistic grounds (Scheme 31). Consequently, the derived primary amine is assigned the 7-aminoquinoxaline structure (374c).

It was of interest to investigate the effect of blocking the 7-position with a chloro substituent to see if substitution would take place elsewhere in the ring. Consequently, the N-hydroxy compound (357d) was treated at room temperature with tosyl chloride in pyridine to give a brown solid whose t.l.c. showed it to be an unresolvable mixture which could not be separated by crystallisation. Also isolated from this reaction was a brown oil whose t.l.c. showed it to be an unresolvable four component mixture which was not investigated further.

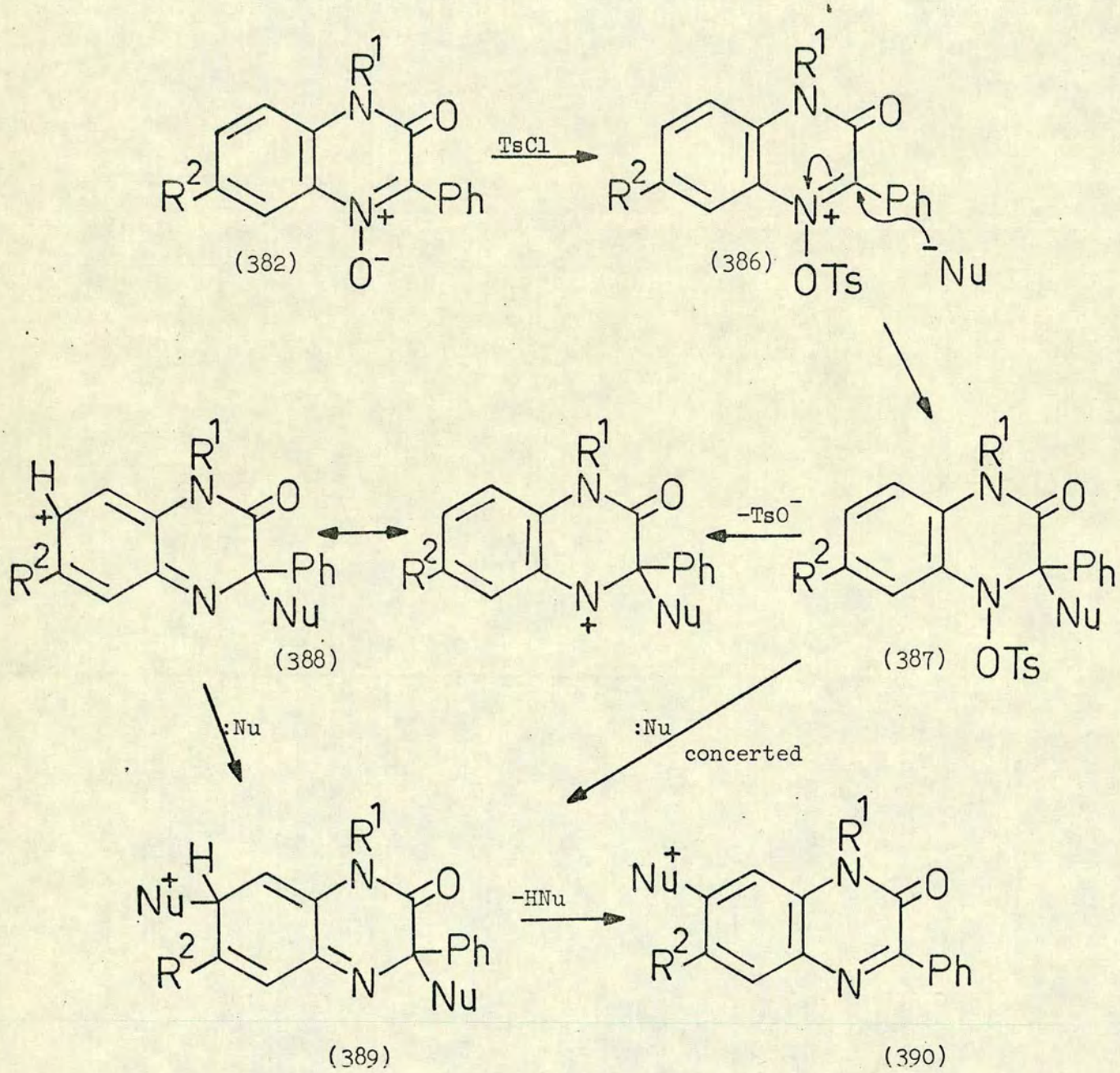
The effect of blocking the 7-position with a methyl group was also investigated to determine whether substitution would occur at the 5-position of the ring or on the 7-methyl group. The reaction of the quinoxaline N-oxide (379a) with acetic anhydride has been shown[230] to afford the 7-acetoxymethyl derivative (380a). The reaction of the 4-hydroxy-7-methylquinoxaline (357e) with tosyl chloride in pyridine yielded mainly unresolvable multi-component mixtures. However, also isolated was a very low yield of a colourless salt whose elemental analysis suggested the molecular formula, $C_{28}H_{25}N_3O_5S$, consistent with the structure (381) or an isomer. The mass spectrum showed a parent ion peak at 344 mass units, consistent with the cation of (381). On the basis of these data and by analogy with (380a) and with the products from the reactions of (379 a and b) with tosyl chloride in pyridine (which will be discussed later), the salt isolated from the reaction of (357e) with tosyl chloride in pyridine is assigned the structure (381).

The successful isolation of the pyridinium betaines (371 a and b) from the reactions of (357 b and c) with tosyl chloride in

pyridine prompted an investigation of the similar reactions of the quinoxalinone 4-oxides (382a-h) which had previously been shown[230,231] to exhibit unusual behaviour in the presence of acylating agents. The quinoxalinone 4-oxides (382a-h) and (379 a and b) and the 1-hydroxyquinoxaline 4-oxides (383 a and b) which were all investigated had been synthesised previously[231].

The reaction of the N-oxide (382a) with tosyl chloride in pyridine at 60° afforded in addition to starting material, a high yield of a pale yellow solid whose elemental analysis was consistent with the molecular formula, $C_{27}H_{23}N_3O_4S$, and whose mass spectrum showed a parent ion peak at m/e 314. These data are in accord with the quinoxalinylpyridinium tosylate structure (384a). The ^1H n.m.r. spectrum of the yellow solid was also consistent with this formulation. This exhibited lowfield aromatic signals at τ0.83 and τ1.06-1.43, indicative of the presence of a pyridine ring. The structure (384a) was confirmed by degradation in good yield to the primary amine (385a) using piperidine in methanol. The structure of (385a) was in turn confirmed by its elemental analysis and by mass, i.r. and ^1H n.m.r. spectral data. First order analysis of the ^1H n.m.r. spectrum showed a 1,2,4-trisubstitution pattern in the fused benzene ring suggesting that the amino group was situated at the 6- or 7-position. The 7-position for substitution was unequivocally established by diazotisation of the amine (385a) and hydrolysis of the derived diazonium salt (385d) (which could be isolated as a yellow solid exhibiting typical multiple bond absorption at 2250 cm^{-1} in its i.r. spectrum) to give in low yield the known[231] phenol (385b), identical to an authentic sample.

Formation of the pyridinium salt (384a) by the reaction of (382a) with tosyl chloride in pyridine can be rationalised by the



Scheme 32

mechanism shown in Scheme 32. This involves nucleophilic attack at the 3-position of the initially formed quaternary salt (386) to give (387) which may further react by either of two pathways. Nucleophilic attack by pyridine at the 7-position of (387) with simultaneous loss of the tosyloxy anion could afford the intermediate (389) directly. Deprotonation and loss of the C-3 substituent from (389) would then yield the product (390). Alternatively, formation of (389) from (387) could be a stepwise process via the resonance-stabilised nitrenium ion (388). As previously mentioned (Chapter 4, Part 2), nitrenium ions have been postulated as intermediates in analogous reactions[219-221] but their existence is still a matter of controversy.

The analogous reaction of the chloro compound (382b) with tosyl chloride in pyridine gave a pale yellow solid in moderate yield in addition to an almost 50% recovery of the starting material. The yellow solid is thought to be the quinoxalinylpyridinium chloride (384b) despite the fact that its elemental analysis suggests a molecular formula containing one oxygen atom and one water molecule more than that predicted for (384b). This type of behaviour has already been encountered in the pyridinium betaines (371 a and b). However, an exact mass determination on the parent ion peak at m/e 348 in the mass spectrum of (384b) suggested a molecular formula, $C_{20}H_{15}ClN_3O$, consistent with the cation of (384b). The ^1H n.m.r. spectrum showed an N-methyl group and twelve aromatic protons, one of which gave rise to a singlet at τ1.33 which is assigned to H-8 since the close proximity of the electron deficient pyridine ring will have a deshielding effect at this site. Thus, on the basis of mass and ^1H n.m.r. spectral data and by analogy with (384a), the product from the reaction of (382b) with tosyl chloride in pyridine is assigned the structure (384b). Also isolated from this reaction was a low yield of a yellow solid shown by t.l.c. to be a two

component mixture. One of the components was identified as the dichloro compound (391a) by mass and ^{1}H n.m.r. spectral data. The mass spectrum of the solid showed peaks at 308, 306 and 304 mass units displaying the characteristic pattern of a molecule containing two chlorine atoms. The ^{1}H n.m.r. spectrum showed a multiplicity of N-methyl signals, confirming the presence of a mixture, but also in the aromatic region, a singlet absorption at τ2.03 which compares well with the absorption of H-8 in the known[231] dichloro compound (391a). The latter compound is presumably formed by a mechanism similar to that shown in Scheme 32, involving nucleophilic attack by chloride ion.

In addition to an almost 50% recovery of starting material, the reaction of the 6-methylquinoxaline (382c) with tosyl chloride in pyridine gave a low yield of a pale yellow salt, assigned, by analogy with (384a) and on spectral grounds, the quinoxalinyl-pyridinium salt structure (384c). As found for (384b), the elemental analysis of the salt (384c) did not correspond to the predicted formula $C_{28}H_{25}N_3O_4S$ but suggested a molecular formula containing an extra oxygen atom. However, high resolution mass spectral analysis of the parent ion peak at m/e 328 in the mass spectrum of (384c) suggested a molecular formula which is consistent with the cation of (384c), as was the ^{1}H n.m.r. spectrum which showed the presence of three methyl groups and a total of sixteen aromatic protons. Consequently, despite the anomalous analytical data, the pale yellow salt is assigned the structure (384c).

Assuming the mechanism shown in Scheme 32, the presence of an electron-donating group in the 6-position (R^2) should inhibit the proposed nucleophilic attack at the 7-position of either of the intermediates (388) or (387). This was found to be the case since heating the 6-methoxy compound (382d) at 60° or under reflux for

24 h with tosyl chloride in pyridine gave only a quantitative recovery of the starting material.

Attention was next focussed on the 1-unsubstituted N-oxides (382e-h). The reaction of (382e) with tosyl chloride in pyridine afforded a colourless salt which on basification yielded an orange solid in moderate yield. The mass spectrum showed a parent ion peak at m/e 300, consistent with the cation (384d). The orange solid is thus thought to be the pyridinium betaine (392a). The mass spectrum of the betaine (371a) also showed a parent ion peak one mass unit higher than the expected molecular weight. The elemental analysis of the orange solid, however, in common with the betaines (371 a and b), suggested a molecular formula-containing one oxygen atom more than that predicted on the basis of the structure (392a). Because of this, an attempt was made to establish the structure (392a) by degradation. Heating the orange solid under reflux in piperidine and methanol afforded a low yield of the primary amine (385c). The elemental analysis and mass, i.r. and ^{1}H n.m.r. spectral data for the product of this reaction were all consistent with the structure (385c). In its ^{1}H n.m.r. spectrum, the NH_2 absorption appears as a broad peak at τ3.80-4.03 and the doublet, showing meta-coupling, centred at τ3.60, and the double doublet, showing ortho- and meta-coupling, centred at τ3.38, are assigned to H-8 and H-6 respectively. Thus, with the exception of the analytical data, all of the available evidence suggests that the orange product from the reaction of (382e) with tosyl chloride in pyridine has the betaine structure (392a).

Also isolated from the reaction of (382e) with tosyl chloride in pyridine was a moderate yield of a yellow solid whose i.r. spectrum suggested it to be mainly starting material. T.l.c. confirmed this but showed the presence of two minor components. The mass spectrum

of this solid showed, in addition to the parent ion peak at m/e 238, corresponding to the starting material (382e), peaks at 256 and 258 mass units, corresponding to the isotopic distribution of a molecule containing a chlorine atom. This suggests that one of the minor components of the mixture is the chloro compound (391c) which is presumably formed by nucleophilic substitution by chloride ion by a mechanism similar to that shown in Scheme 32.

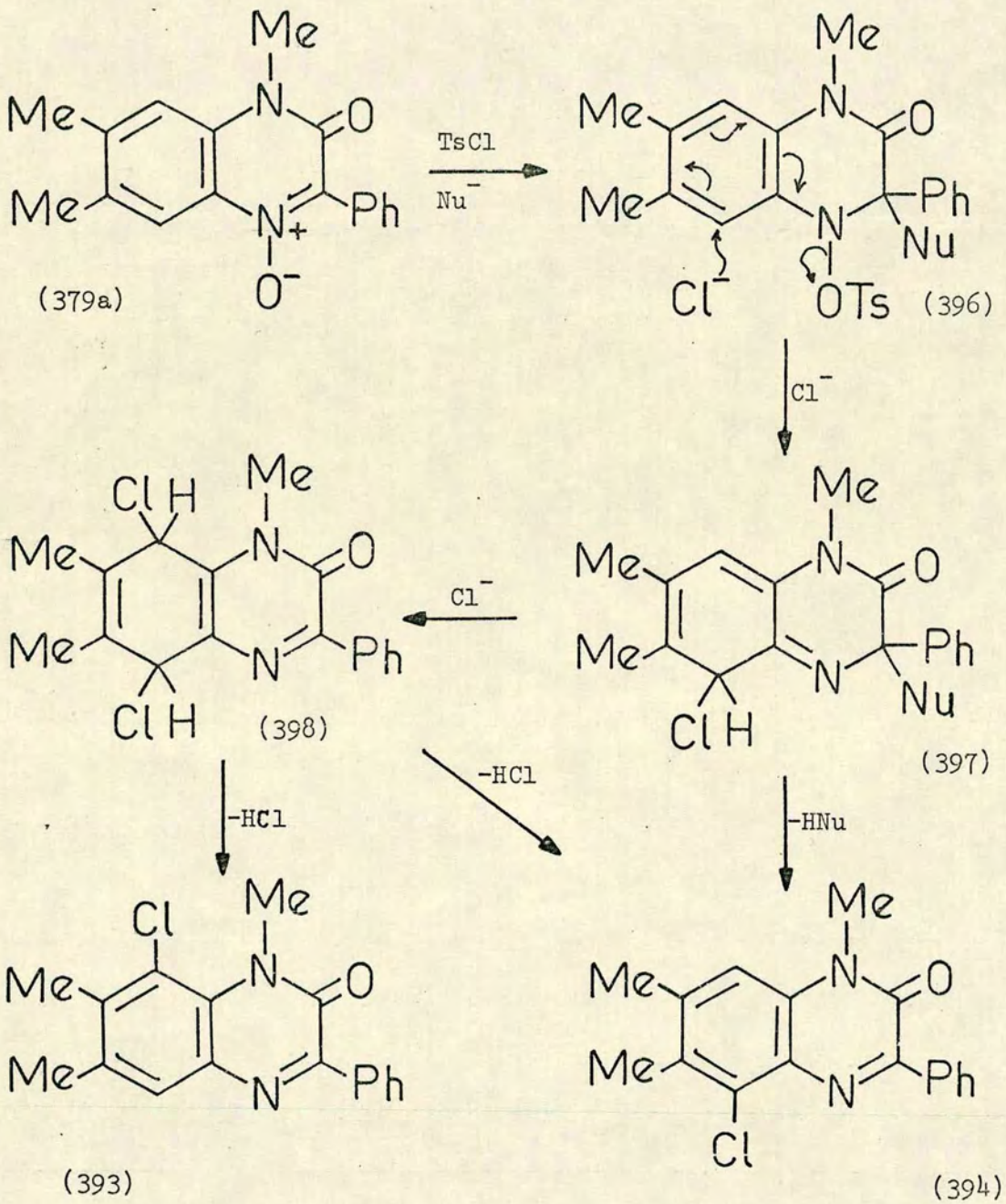
The analogous reaction of the chloro compound (382f) with tosyl chloride in pyridine afforded a low yield of a yellow solid assigned the betaine structure (392b) by analogy with (392a) and the salts (384a-c) and on the basis of analytical and spectral data. However, the elemental analysis of this product was consistent with that of a monohydrate of the betaine (392b). Also, the mass spectrum did not show the parent ion peak. The ^{1}H n.m.r. spectrum contained two singlet aromatic absorptions at τ1.52 and 1.87 which can be assigned in the absence of ortho- or meta-coupling to H-8 and H-5 respectively confirming that the 7-position is substituted. Also isolated from this reaction was a yellow solid whose t.l.c. showed it to contain mainly the starting material (382f) but also three other minor components, one of which is thought on spectral grounds to be the dichloro compound (391d). The mass spectrum of the mixture showed peaks at 294, 292 and 290 mass units, corresponding to the isotopic distribution of a molecule containing two chlorine atoms. The ^{1}H n.m.r. spectrum of the mixture showed a meta-coupled doublet centred on τ1.48, corresponding to H-5 of the starting material (382f) and a singlet at τ1.72 corresponding well with the reported[231] value assigned to H-5 of the dichloro compound (391d). The latter compound is presumably formed in a similar manner to (391c).

Like (392b), the elemental analysis of the yellow product obtained in good yield from the reaction of (382g) with tosyl

chloride in pyridine suggested it to be a monohydrate of the betaine (392c). Its mass spectrum showed a parent ion peak at m/e 314, corresponding to the derived cation (384e). Its ^{1}H n.m.r. spectrum was also consistent with this assignment, showing a methyl group and a total of twelve aromatic protons, one of which appears as a singlet at τ1.97, attributable to H-5. The remainder of the material isolated in low yield was shown by comparison with an authentic sample[231] to be the chloro compound (391e), presumably formed in a similar manner to (391c) and (391d).

Unlike the 6-methoxy compound (382d), which failed to react, heating the corresponding 1-unsubstituted compound (382h) with tosyl chloride in pyridine afforded in addition to a high yield of the starting material a very low yield of an orange solid which is thought to be the betaine (392d). Its mass spectrum does not show the parent ion and elemental analysis suggests a molecular formula containing four hydrogen atoms and four oxygen atoms more than that expected for the betaine (392d). However, the ^{1}H n.m.r. spectrum of this product is consistent with the structure (392d), showing a methoxyl group and a total of twelve aromatic protons. The lack of material prevented any further experiments to establish rigorously the structure of this product.

As mentioned previously, the 6,7-dimethylquinoxaline N-oxide (379a) undergoes acetoxylation[230] of the 7-methyl group on heating with acetic anhydride. Thus, it was of interest to investigate the reactions of the N-oxides (379 a and b) with tosyl chloride in pyridine to ascertain whether substitution occurs at the ring or on the methyl group. Prolonged treatment of the N-methyl compound (379a) with tosyl chloride in pyridine afforded in good yield a yellow solid whose t.l.c. showed it to be a two component mixture. Separation of the mixture by column chromatography gave, as the

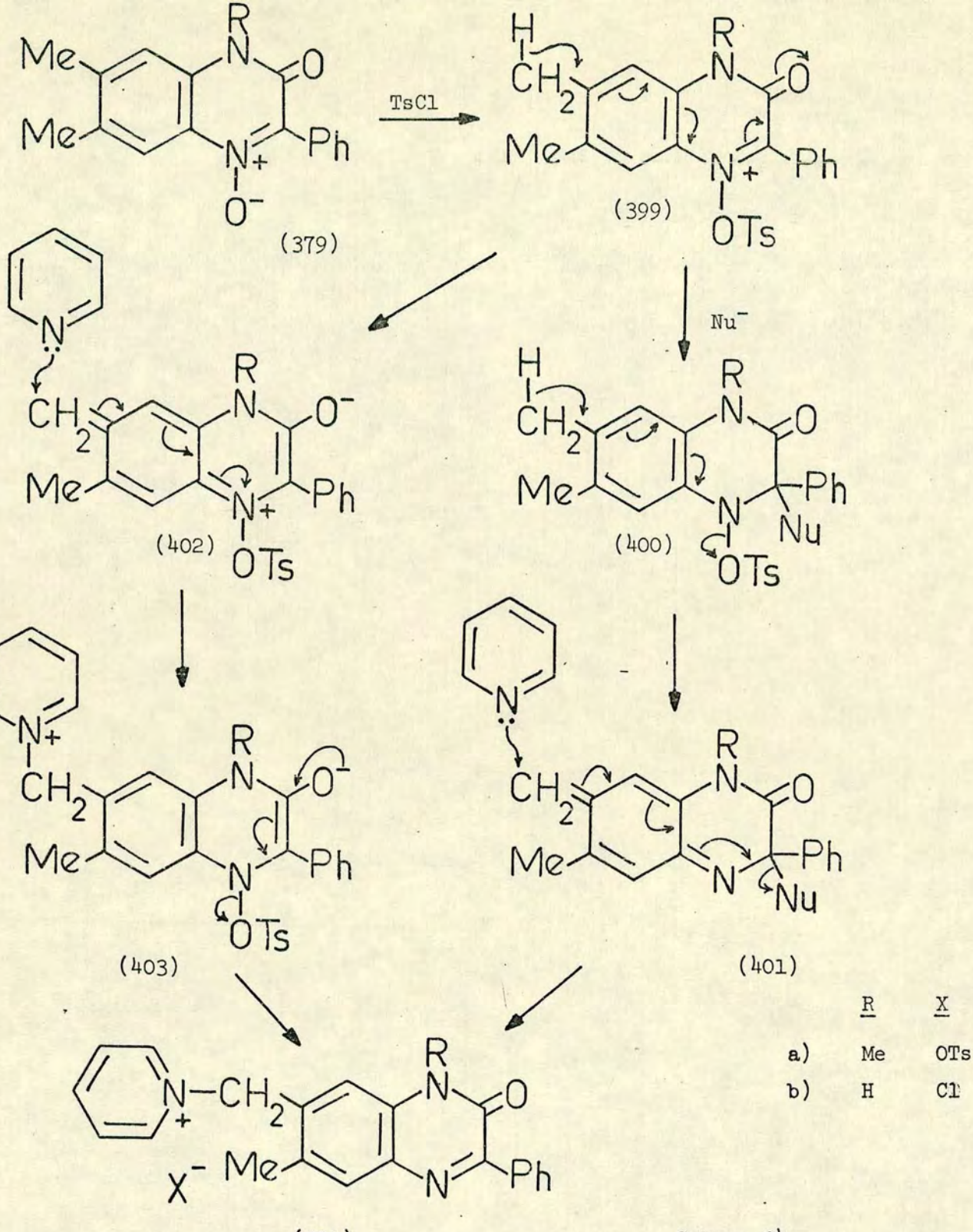


(379a) (396) (398) (397) (393) (394)

Scheme 33

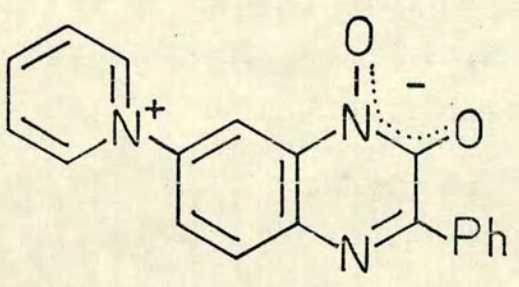
faster-moving component, the 8-chloro compound (393) and, as the slower-moving component, its 5-chloro isomer (394). The products were shown to be identical to the known[209] compounds by comparison of their ^{1}H n.m.r. and i.r. spectra and by mixed melting point. The formation of these products can be explained by the mechanism shown in Scheme 33 in which the important step is the nucleophilic attack by chloride ion at the 5-position of the intermediate (396) with concomitant loss of the tosyloxy anion to give the adduct (397). Formation of (397) can also be visualised as a stepwise process involving a nitrenium ion. Deprotonation and loss of the substituent from the 3-position of (397) then affords the 5-chloro isomer (394). Conversely, further nucleophilic attack by chloride ion would give the dichloro intermediate (398) which is capable of eliminating hydrogen chloride in two possible ways to give the two isomers (393) and (394).

Also isolated from the reaction of (379a) with tosyl chloride in pyridine was a small quantity of a pale yellow solid whose elemental analysis indicated the molecular formula $C_{29}H_{27}N_3O_4S$. Its ^{1}H n.m.r. spectrum showed a total of sixteen aromatic protons, an N-methyl group, one ring methyl group, the methyl group of a tosyloxy substituent and a two-proton singlet at τ3.77, assigned to a methylene group. These data are consistent with the quinoxalinylmethylpyridinium salt (395a) which is thought to be formed by the mechanism shown in Scheme 34. Proton abstraction from the initially formed N-tosyloxy salt (399) affords the zwitterionic intermediate (402). Nucleophilic attack by pyridine at the methylene group affords (403) which readily loses the tosyloxy anion to afford the product (395). Alternatively, nucleophilic attack at the 3-position of (399) could afford (400). Proton abstraction from (400) with loss of the tosyloxy anion would then yield (401) which on nucleophilic attack by pyridine,

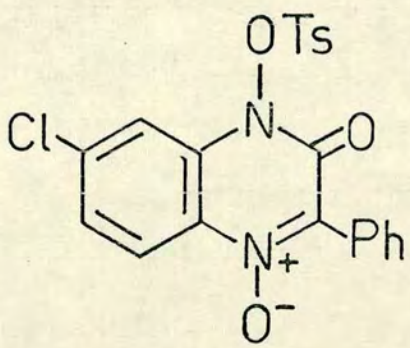


	R	X
a)	Me	OTs
b)	H	Cl

Scheme 34



(404)



(405)

with loss of the nucleophile from the 3-position of (401), would lead to the product (395). Without further evidence, it is impossible to distinguish between these possible mechanisms.

The analogous quinoxalinylmethylpyridinium chloride (395b) was isolated in good yield from the reaction of (379b) with tosyl chloride in pyridine. Elemental analysis suggested that the product was a monohydrate of the chloride (395b) and the structure was confirmed by its ^{1}H n.m.r. spectrum, which showed one methyl group, a total of twelve aromatic protons and absorption at $\tau 3.84$ due to a methylene group. (395b) is presumed to be formed by a mechanism similar to those shown in Scheme 34. The formation of (395 a and b) lends support to the structure (381) proposed for the product of the reaction of (357e) with tosyl chloride in pyridine (p.153).

The 1-hydroxyquinoxaline 4-N-oxides (383 a and b) were also of interest since they contain two N-oxo functions which may be capable of participation in nucleophilic substitution reactions. The reaction of (383a) with tosyl chloride in pyridine gave a colourless salt which on basification yielded an orange solid, which is assigned the pyridinium betaine structure (404) on the basis of its elemental analysis and mass spectrum and on mechanistic grounds. The elemental analysis is consistent with a monohydrate of (404) and the mass spectrum shows a parent ion peak one mass unit greater than the molecular weight of (404), a feature also exhibited by the betaines (392 a and c). The betaine (404) is presumably formed in an analogous manner to the betaines (392 a-c) (cf. Scheme 32). The remainder of the material isolated from this reaction was a multi-component mixture from which was obtained an unidentified solid, whose mass spectrum and elemental analysis could not be reconciled with any simple structure.

The reaction of (383b) with tosyl chloride took a completely different course, possibly because the 7-position is blocked to

nucleophilic attack. The N-tosyloxy compound (405) was isolated in quantitative yield. The elemental analysis and mass and ^{1}H n.m.r. spectrum were consistent with the structural assignment (405) which was confirmed by alkaline hydrolysis to the N-hydroxy compound (383b). Performing the reaction of (383b) with tosyl chloride in pyridine at a higher temperature produced a diminished yield of (405) in addition to multi-component mixtures.

The success of the rearrangements of the N-tosyloxyquinazolinediones (313a-c) (cf. Chapter 4, Part 2) prompted an investigation of the similar rearrangement of the N-tosyloxyquinoxaline (405). However, heating (405) under reflux in glacial acetic gave only a dark intractable oil, shown by t.l.c. to be a multi-component mixture. On the other hand, stirring (405) at room temperature in glacial acetic acid in the presence of fused sodium acetate failed to induce any reaction giving an almost quantitative recovery of the starting material (405).

CHAPTER FIVE

EXPERIMENTAL

PART 1

1-Hydroxy-2-methylquinolin-4(1H)-ones

1. The Reactions of 2-Nitrobenzaldehyde with Active Methylene Compounds in the Presence of Hydrogen Chloride.

(i) The condensation of 2-nitrobenzaldehyde with acetylacetone in ethereal hydrogen chloride[202] gave 3-acetyl-6-chloro-1-hydroxy-2-methylquinolin-4(1H)-one (271a), (59%), m.p. 281-286° (decomp.) [lit.,[202] 286° (decomp.)], $\nu_{max.}$ 2800-2400 (br) (N-OH) and 1680 and 1590 (CO) cm^{-1}, which gave a deep red colour in the presence of iron (III) chloride. Evaporation of the ether mother liquors, treatment with saturated aqueous sodium bicarbonate and extraction with chloroform gave 3-(2'-nitrobenzylidene)pentane-2,4-dione (273a), (35%), m.p. 67-72° (lit.,[202] 76°).

(ii) The condensation of 2-nitrobenzaldehyde with ethyl acetoacetate in ethereal hydrogen chloride[202] gave 6-chloro-3-ethoxycarbonyl-1-hydroxy-2-methylquinolin-4(1H)-one (271b), (64%), m.p. 218-222° (decomp.)[lit.,[202] 226° (decomp.)], $\nu_{max.}$ 2700-2350 (br) and 1720 and 1590 (CO) cm^{-1}, which gave a deep red colour in the presence of iron (III) chloride. Evaporation of the ether mother liquors, treatment with saturated aqueous sodium bicarbonate and extraction with chloroform gave a brown oil, (34%), whose ^1H n.m.r. spectrum, τ (60 MHz) ($CDCl_3$) 1.60-1.97 (6 units, m, ArH), 2.10-2.75 (10 units, m, ArH), 5.65 (2 units, q, J 7 Hz, CH_2), 5.90 (4 units, q, J 7 Hz, CH_2), 7.51 (6 units, s, COMe), 7.77 (3 units, s, COMe), 8.63 (3 units, t, Me) and 9.00 (6 units, t, Me), showed it to be a 2:1 mixture of the geometric isomers (273b) and (273c) of ethyl 2-(2'-nitrobenzylidene)acetoacetate, (lit.,[232] oil, [48] m.p. 69°).

(iii) A solution of benzoylacetone (1.62g, 0.01 mol) and 2-nitrobenzaldehyde (1.51g, 0.01 mol) in sodium-dried ether (20 ml)

was saturated with hydrogen chloride and left at room temperature for 66h. The orange solution was washed with dilute aqueous sodium hydroxide solution (2x10 ml) and the washings were acidified to give unreacted benzoylacetone (1.10g, 68%), identical (m.p. and i.r. spectrum) to the starting material. The ether layer was washed with saturated aqueous sodium bisulphite (2x15 ml) and the bisulphite complex of 2-nitrobenzaldehyde was collected, hydrolysed by heating under reflux (5 min.) with dilute aqueous sulphuric acid and extracted with chloroform to give 2-nitrobenzaldehyde, (0.75g, 50%), identical (m.p. and i.r. spectrum) to the starting material. Evaporation of the ether layer under reduced pressure gave 2-(2'-nitrobenzylidene)-1-phenylbutane-1,3-dione (273d), (0.68g, 28%), as an oil which solidified on scratching and cooling, m.p. 55-68° (lit.,[233] 77°). The benzylidene compound (273d) was also prepared (40%) by the reaction of benzoylacetone (5.4g, 0.033 mol) with 2-nitrobenzaldehyde (3.75g, 0.025 mol) in glacial acetic acid (10 ml) in the presence of piperidine (2.4 ml) at room temperature for 70h. Also isolated were unreacted benzoylacetone (3.03g, 0.019 mol) and unreacted 2-nitrobenzaldehyde (31%).

A solution of the benzylidene compound (273d) (2.95g, 0.01 mol) in sodium-dried ether (100 ml) was saturated with hydrogen chloride and left at room temperature for 144h. Evaporation of the mixture under reduced pressure and trituration with ether-light petroleum gave the unreacted benzylidene compound (273d), (2.66g, 90%), identical (m.p. and i.r. spectrum with an authentic sample.

(iv) A solution of 2-nitrobenzaldehyde (1.50g, 0.01 mol) and indane-1,3-dione (1.46g, 0.01 mol) in sodium-dried ether (175 ml) was saturated with hydrogen chloride and the mixture was left at room temperature for 25h. Evaporation under reduced pressure, treatment with saturated aqueous sodium bicarbonate and extraction with

chloroform gave a red oily solid which was triturated with ether and crystallised from glacial acetic acid to give 2-(2'-nitrobenzylidene)-indane-1,3-dione (276), (1.26g, 45%), as yellow needles, m.p. 184-186° (decomp.), (lit.,[204] 183°).

Found: C,68.9%; H,3.2%; N,4.4%; M^+279.

Calc. for $C_{16}H_9NO_4$: C,68.8%; H,3.3%; N,5.0%; M 279.

Acidification of the bicarbonate washings and extraction with chloroform gave a brown gum (0.50g) whose t.l.c. in chloroform over silica showed it to be a multi-component mixture.

(v) A solution of 2-nitrobenzaldehyde (1.50g, 0.01 mol) and ethyl cyanoacetate (1.13g, 0.01 mol) in glacial acetic acid (30 ml) was saturated with hydrogen chloride and left at room temperature for 48h. Evaporation of the solvent under reduced pressure, treatment with saturated aqueous sodium bicarbonate and extraction with chloroform gave an orange oil (1.81g) which was triturated with ether to give a mixture of the geometric isomers (273e) and (273f) of ethyl 2-(2'-nitrobenzylidene)malonamate, (0.55g, 21%), as colourless prisms, m.p. 87-115° (from ethanol - light petroleum), $\nu_{max.}$ 3400 and 3120 (NH), 1705 and 1670 (CO) and 1530 and 1340 (NO_2) cm^{-1}.

Found: C,55.7%; H,4.6%; N,10.7%.

$C_{12}H_{12}N_2O_5$ requires: C,55.6%; H,4.6%; N,10.6%.

Acidification of the aqueous layer and extraction with chloroform gave an unidentified yellow oil (0.23g).

(vi) Toluene-4-sulphonyl acetone prepared from sodium toluene-4-sulphinate dihydrate and chloroacetone using the method of Otto and Otto[205] (75%) had m.p. 41-46° (lit.,[205] 51°).

A solution of 2-nitrobenzaldehyde (1.50g, 0.01 mol) and toluene-4-sulphonylacetone (2.12g, 0.01 mol) in sodium-dried ether (20 ml) was saturated with hydrogen chloride and left at room temperature for 70h. The ether solution was washed with saturated

aqueous sodium bicarbonate and evaporated under reduced pressure to give a yellow oil (3.55g) whose t.l.c. in chloroform over silica showed it to be a mixture of the two starting materials.

(vii) A solution of 2-nitrobenzaldehyde (1.50g, 0.01 mol) and dimedone (1.40g, 0.01 mol) in glacial acetic acid (30 ml) was saturated with hydrogen chloride and left at room temperature for 24h. Evaporation of the dark solution and trituration of the residue with ether yielded a pale yellow solid which on crystallisation gave dimedone, (0.88g, 63%), identical (m.p. and i.r. spectrum) to an authentic sample. The trituration liquors were washed with saturated aqueous sodium bisulphite and evaporated under reduced pressure to give a red gum (0.40g). Acidification of the aqueous layer and extraction with chloroform gave a yellow solid (0.60g). T.l.c. in chloroform or chloroform-methanol over silica showed that the solid and the gum were multi-component mixtures.

2. The Reactions of 3-Acetyl-6-chloro-1-hydroxy-2-methylquinolin-4(1H)-one (271a) with Acid Anhydrides.

(i) The N-hydroxyquinolinone (271a) (3.0g, 0.012 mol) was heated at 100° with acetic anhydride (5.0 ml) for 20 min. and the mixture was cooled and triturated with ether to give 1-acetoxy-3-acetyl-6-chloro-2-methylquinolin-4(1H)-one (272a), (2.9g, 83%), m.p. 162-165° (lit.,[202] 166°), $\nu_{max.}$ 1795, 1675 and 1625 (CO) cm^{-1}. Evaporation of the mother liquors under reduced pressure and trituration with ether - light petroleum gave a brown solid (0.52g) which was shown by t.l.c. in chloroform-methanol over silica to be a mixture of the N-acetoxyquinolinone (272a) and another component which was subsequently identified as the 2-(acetoxymethyl)quinolinone (277a).

(ii) The N-hydroxyquinolinone (271a) (0.75g, 0.003 mol) was heated at 100° with acetic anhydride (1.3 ml) for 6h. Evaporation of the mixture under reduced pressure and trituration with ether gave a brown solid (0.17g) whose t.l.c. in chloroform-methanol over silica showed it to be a mixture of an unidentified fluorescent component and a second component which was subsequently shown to be the 2-(acetoxymethyl)-quinolinone (277a). Evaporation of the mother liquors under reduced pressure, treatment with water and extraction with chloroform gave a yellow oil (0.48g) whose t.l.c. in chloroform-methanol over silica showed it to contain, in addition to the above two components, the N-acetoxy compound (272a).

(iii) The N-hydroxyquinolinone (271a) (1.00g, 0.004 mol) was heated at 100° with propionic anhydride (2.0 ml) for 20 min. and the mixture was cooled and triturated with ether to give 3-acetyl-6-chloro-2-methyl-1-propionyloxyquinolin-4(1H)-one (278), (0.85g, 70%), as colourless needles, m.p. 138-140° (decomp.) (from ethanol), $\nu_{max.}$ 1790, 1675 and 1625 (CO) cm^{-1}, τ ($CDCl_3$) 1.68 (1H, d, J_{meta} 2 Hz, H-5), 2.43 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-7), 2.87 (1H, d, J_{ortho} 9 Hz, H-8), 7.20 (2H, q, J 8 Hz, CH_2), 7.37 (3H, s, COMe), 7.64 (3H, s, ArMe) and 8.62 (3H, t, J 8 Hz, CH_2-Me).

Found: C,58.5%; H,4.6%; N,4.8%; M^+307.

$C_{15}H_{14}ClNO_4$ requires: C,58.6%; H,4.6%; N,4.6%; M 307.

Evaporation of the mother liquors under reduced pressure and trituration with ether-light petroleum gave a brown solid (0.20g) whose t.l.c. in chloroform or chloroform-methanol over silica showed it to be a mixture of starting material, the N-propionyloxyquinolinone (278) and a third component which was subsequently identified as the 2-(propionyloxymethyl)quinoline (277b).

3. The Reactions of the N-Acyloxy Compounds (272a) and (278) with Glacial Acetic Acid and Propionic Acid.

(i) The N-acetoxyquinolinone (272a) (2.64g, 0.009 mol) was heated under reflux in glacial acetic acid (20 ml) for 30 min. and the mixture was evaporated under reduced pressure to give a dark oil which on trituration with ether gave a very dark solid (2.55g), $\nu_{max.}$ 1740 and 1680 (CO) cm^{-1}. Soxhlet extraction of the dark solid with benzene for 18h afforded 2-acetoxymethyl-3-acetyl-6-chloroquinolin-4(1H)-one (277a), (1.19g, 45%), as a pale brown solid which decomposes without melting in the range 175-182° and was crystallised from ethanol-light petroleum to give colourless plates which decomposed without melting from 178-187°, $\nu_{max.}$ 3100-2600 (OH) and 1740 and 1690 (CO) cm^{-1}, τ ($CDCl_3$) 1.77 (1H, d, J_{meta} 2 Hz, H-5), 2.26-2.51 (2H, m, ArH), 4.68 (2H, s, CH_2), 7.35 (3H, s, COMe) and 7.84 (3H, s, OCOMe).

Found: C,57.2%; H,4.2%; N,5.0%; M^+293.

$C_{14}H_{12}ClNO_4$ requires: C,57.3%; H,4.1%; N,4.8%; M 293.

The insoluble residue from the Soxhlet extraction was a black intractable solid (1.20g).

(ii) The N-propionyloxyquinolinone (278) (0.31g, 0.001 mol) was heated in propionic acid (7.5 ml) at 100° for 1.75h. The solvent was evaporated under reduced pressure and the dark residue was leached with boiling benzene (2x75 ml) and hot filtered to remove a black intractable solid (0.07g). Evaporation of the benzene extract under reduced pressure gave 3-acetyl-6-chloro-2-(propionyloxymethyl)quinolin-4(1H)-one (277b), (2.19g, 61%), as a pale orange solid which decomposed without melting in the range 168-175°. Crystallisation from ethanol-light petroleum afforded colourless plates, which decomposed without melting from 172°-181°, $\nu_{max.}$ 3100-2600 (OH), and 1740 and 1690 (CO) cm^{-1}, τ ($CDCl_3$) 1.69-1.76 (1H, m, ArH), 2.40-2.48 (2H, m, ArH), 4.65 (2H, s,

CH_2-O), 7.32 (3H, s, COMe), 7.52 (2H, q, J 8 Hz, $\underline{CH_2}$-Me) and 8.84 (3H, t, J 8 Hz, CH_2-$\underline{Me}$).

Found:	C,58.6%; H,4.7%; N,4.7%; M^+307.
$C_{15}H_{14}ClNO_4$ requires:	C,58.6%; H,4.6%; N,4.6%; M 307.

(iii) The N-propionyloxyquinolinone (278) (0.31g, 0.001 mol) was heated under reflux in glacial acetic acid (5.0 ml) for 30 min. The dark solution was evaporated under reduced pressure and the dark residue (0.27g) was collected by trituration with ether and leached with boiling benzene with hot filtration to remove a dark brown intractable solid (0.09g). Evaporation of the benzene extract under reduced pressure gave a pale brown solid (0.14g), m.p. 156-168° (decomp.), $\nu_{max.}$ 3100-2600 (OH) and 1740 and 1690 (CO) cm^{-1}, whose ^1H n.m.r. spectrum, τ ($CDCl_3$) -1.39 (10 units, br s, OH), 1.79 (10 units, d, J_{meta} 2 Hz, H-5), 2.27-2.40 (20 units, m, ArH), 4.69 (20 units, s, CH_2), 7.35 (30 units, s, COMe), 7.55 (15 units, q, J 8 Hz, $\underline{CH_2}$-Me), 7.84 (9 units, s, OCOMe) and 8.86 (22 units, t, J 8 Hz, CH_2-$\underline{Me}$), showed it to be a 1:2 mixture of the 2-(acetoxymethyl)quinoline (277a) and the 2-(propionyloxymethyl)-quinoline (277b).

(iv) The N-acetoxyquinolinone (272a) (0.59g, 0.002 mol) in propionic acid (15 ml) was heated at 100° for (a) 30 min and (b) 1.75h.

Cooling the dark mixture in case (a) gave the N-hydroxyquinolinone (271a) (0.13g, 25%), identical (i.r. spectrum) to an authentic sample. Evaporation of the filtrate under reduced pressure and trituration with ether gave a brown solid (0.35g), $\nu_{max.}$ 1790, 1740, 1675 and 1625 (CO) cm^{-1}, whose ^1H n.m.r. spectrum, τ (60 MHz) ($CDCl_3$) 1.67 (13 units, d, J_{meta} 2 Hz, H-5), 2.25-2.97 (26 units, m, ArH), 4.53 (9 units, s, CH_2), 7.18 (16 units, q, J 8 Hz, $\underline{CH_2}$-Me), 7.30 (13 units, s, COMe), 7.37 (26 units, s, COMe), 7.63 (26 units, s, ArMe), 8.60 (26 units, t, J 8 Hz, CH_2-$\underline{Me}$) and 8.80 (12 units, t, J 8 Hz, CH_2-$\underline{Me}$), showed it to be a 2:1 mixture of the N-propionyloxyquinolinone (278) and the 2-(propionyloxy-methyl)quinolinone (277b).

Cooling the dark solution in case (b) gave the N-hydroxyquinolinone (271a) (0.10g, 20%), identical (i.r. spectrum) to an authentic sample. Evaporation of the filtrate under reduced pressure and trituration of the residue with ether-light petroleum gave a dark solid (0.42g) which was leached with boiling benzene with hot filtration to remove a dark brown intractable solid (0.11g). Evaporation of the benzene extract under reduced pressure gave a pale orange solid (0.27g), identical (i.r. and ^{1}H n.m.r. spectrum) to the solid mixture of the acyloxymethylquinolinones (277 a and b) obtained in (iii).

4. The Attempted Thermolysis of the N-Acetoxyquinolinone (272a) in Boiling Toluene.

The N-acetoxyquinolinone (272a) (0.30g, 0.001 mol) was heated under reflux in sodium-dried toluene (20 ml) for 30 min. The solution was cooled and scratched to afford the starting material (272a) which was combined with a further crop obtained by evaporation of the mother liquors under reduced pressure (total 0.28g, 93%) and was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

5. The Attempted Reaction of the N-Acetoxyquinolinone (272a) with Hydrogen Chloride.

A solution of the N-acetoxyquinolinone (272a) (0.30g, 0.001 mol) in absolute ethanol (60 ml) was saturated with hydrogen chloride and left at room temperature for 20h. Evaporation of the mixture under reduced pressure, treatment of the residue with saturated aqueous sodium bicarbonate and acidification gave the N-hydroxyquinolinone (271a) (0.25g, quantitative), identical (m.p. and i.r. spectrum) to an authentic sample.

6. The Reaction of the N-Acetoxyquinolinone (272a) with Acetic Acid in Ethanol.

The N-acetoxyquinolinone (272a) (0.59g, 0.002 mol) was heated under reflux in absolute ethanol (10 ml) and glacial acetic acid (0.13 ml, 0.0022 mol) for 2h and cooled to give the N-hydroxyquinolinone (271a) (0.45g, 90%), identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the filtrate under reduced pressure and trituration of the residue with ether gave a pale yellow solid (0.10g) whose t.l.c. in chloroform-methanol over silica showed it to be a three component mixture comprising the N-hydroxyquinolinone (271a), the 2-(acetoxymethyl)-quinolinone (277a) and a third unidentified compound.

7. The Reaction of the N-Hydroxyquinolinone (271a) with Acetyl Chloride in Glacial Acetic Acid.

The N-hydroxyquinolinone (271a) (1.04g, 0.004 mol) was heated under reflux with acetyl chloride (10 ml) and glacial acetic acid (6.0 ml) for 2.5h. Evaporation of the dark brown solution under reduced pressure, treatment with water (10 ml) and extraction with chloroform gave a very dark oil which yielded a dark solid (1.06g) on trituration with ether. Evaporation of the ether mother liquors gave a red oil (0.18g).

Soxhlet extraction of the dark solid with light petroleum for 16h left a very dark intractable residue (0.63g) whose t.l.c. in chloroform-methanol over silica or in ethyl acetate over activity III alumina showed it to be a three component mixture containing the 2-(acetoxymethyl)quinoline (277a) and a yellow fluorescent compound. Evaporation of the light petroleum extract under reduced pressure gave an orange solid (0.45g) whose t.l.c. (as before) showed it to be a two component mixture comprising the 2-(acetoxymethyl)quinolinone (277a) and the yellow fluorescent compound. Dry-column chromatography

of the orange solid in ethyl acetate over alumina gave,

a) an unidentified orange oil (0.08g),

b) 9-chloro-5-hydroxymethyl-2-methyl-4H-pyrano[3,2-c]quinolin-4-one (283), (0.11g, 10%), as bright yellow needles, sublimes 287° (decomp.) (from glacial acetic acid), $\nu_{max.}$ 3150 (OH) and 1640 (CO) cm^{-1},

Found: C,60.5%; H,3.8%; N,5.1%; M^+ 275.

$C_{14}H_{10}ClNO_3$ requires: C,61.0%; H,3.7%; N,5.1%; M 275.

c) a solid two component mixture (0.03g) which was not further investigated,

d) a brown solid (0.21g) whose t.l.c. (as before) showed it to be a two component mixture which could not be purified by crystallisation.

8. The Reactions of the N-Hydroxyquinolines (271 a and b) with Sulphonyl Chlorides in the Presence of Pyridine.

Suspensions of the N-hydroxyquinolines (271 a and b) (0.005 mol) in pyridine (20 ml) were treated with stirring at room temperature with methanesulphonyl chloride or toluene-4-sulphonyl chloride (0.006 mol). The solid dissolved, heat was evolved and the solution darkened. After stirring for 24-54h, the reaction mixtures contained a colourless solid and were worked up as described below.

(i) The mixture obtained by treating the 3-acetylquinolinone (271a) with toluene-4-sulphonyl chloride (1.14g) in pyridine for 54h was evaporated and treated with chloroform, yielding a colourless solid (0.93g) which on crystallisation from dimethylformamide gave the pure 6-chloro-3-hydroxy-1-(toluene-4'-sulphonyl)quinolin-4(1H)-one (286), (0.81g, 45%), as colourless plates, m.p. 270-271° (decomp.), $\nu_{max.}$ 3100-2600 (OH) and 1635 w (CO) cm^{-1}, τ (CF_3CO_2H) 1.52 (1H, s, H-5), 1.91-2.11 (4H, m, ArH), 2.44 (2H, d, J_{ortho} 8 Hz, ArH), 7.30 (3H, s,

ArMe) and 7.46 (3H, s, ArMe).

Found: C,55.6%; H,3.9%; N,3.9%; M^+363.

$C_{17}H_{14}ClNO_4S$ requires: C,56.2%; H,3.9%; N,3.9%; M 363.

After washing with dilute aqueous sulphuric acid (2x15 ml) and dilute aqueous sodium hydroxide (20 ml), the chloroform mother liquors gave the N-acetoxyquinoline (272a) (0.30g, 21%), as a pale brown solid, identical (m.p. and i.r. spectrum) to an authentic sample. Acidification of the sodium hydroxide washings gave a brown solid (0.43g) which was washed with 2N sodium carbonate solution to leave an intractable brown solid (0.21g). Acidification of the sodium carbonate washings gave the starting N-hydroxyquinoline (271a) (0.20g, 16%), identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) Filtration of the mixture from the reaction of the acetylquinolinone (271a) with methanesulphonyl chloride in pyridine for 30h gave a colourless salt (0.26g) which was dissolved in water, washed with chloroform, basified with solid sodium bicarbonate and extracted with a large volume of chloroform to give an unidentified yellow solid which on crystallisation from chloroform-petrol gave yellow prisms which decomposed without melting from 220-230°, τ (CF_3CO_2H) 1.02-1.25 (3H, m, ArH), 1.47-1.73 (3H, m, ArH), 1.94-2.22 (2H, m, ArH) and 7.42 (3H, s, ArMe).

Found: C,58.1%; H,4.2%; N,8.8%.

The pyridine solution was evaporated under reduced pressure and the oily residue was treated with chloroform and dilute aqueous sulphuric acid, to give an insoluble brown solid (0.45g) which on crystallisation from aqueous acetic acid gave 6-chloro-3-hydroxy-1-methanesulphonyl-2-methylquinolin-4(1H)-one (300), (0.28g, 20%), as colourless needles, 285-287° (decomp.), $\nu_{max.}$ 3100-2600 (OH) and 1640 w (CO) cm^{-1}, τ (CF_3CO_2H) 1.51 (1H, s, H-5), 1.99 (2H, s, ArH), 6.38 (3H, s, SO_2Me) and 7.01 (3H, s, ArMe).

Found: C,46.0%; H,3.5%; N,4.9%; M^+287.

$C_{11}H_{10}ClNO_4S$ requires: C,45.9%; H,3.5%; N,4.9%; M 287.

The chloroform extract was washed with dilute aqueous sodium hydroxide (15 ml) and evaporated to give a negligible quantity of red oil. Acidification of the alkaline washings and extraction with chloroform gave a pale brown solid (0.53g) which on crystallisation from ethanol-dimethylformamide gave 3-acetyl-6-chloro-8-(methanesulphonyloxy)quinolin-4(1H)-one (301), (0.27g, 17%), as colourless prisms, m.p. 228-230° (decomp.), $\nu_{max.}$ 3200-2600 (NH) and 1700 and 1635 (CO) cm^{-1}, τ (CF_3CO_2H) 1.45 (1H, d, J_{meta} 2 Hz, H-5), 1.85 (1H, d, J_{meta} 2 Hz, H-7), 6.44 (3H, s, SO_2Me), 6.68 (3H, s, ArMe) and 7.04 (3H, s, COMe).

Found: C,47.2%; H,3.6%; N,4.5%; M^+329.

$C_{13}H_{12}ClNO_5S$ requires: C,47.4%; H,3.7%; N,4.3%; M 329.

(iii) The mixture from the reaction of the 3-ethoxycarbonylquinolinone (271b) with toluene-4-sulphonyl chloride in pyridine for 24h, on evaporation and trituration with acetone, gave a pale brown salt (0.43g) which was dissolved in water (15 ml), basified with solid sodium bicarbonate and extracted with a large volume of chloroform to give an unidentified orange solid (0.15g) which could not be crystallised for characterisation.

Evaporation of the acetone mother liquors under reduced pressure, treatment with dilute aqueous sulphuric acid and extraction with chloroform afforded a dark brown oil (1.41g) which on trituration with chloroform gave 6-chloro-3-hydroxy-2-methyl-1-(toluene-4'-sulphonyl)-quinolin-4(1H)-one (286), (0.09g, 5%), identical (m.p. and i.r. spectrum) to a sample prepared as described in (i) above. The chloroform mother liquors were washed with dilute aqueous sodium hydroxide and evaporated to give a dark brown oil (0.92g) whose t.l.c. in chloroform-methanol

over silica showed it to be a multi-component mixture. Acidification of the alkaline washings and extraction with chloroform gave an intractable red gum (0.30g).

(iv) The mixture from the reaction of the 3-acetylquinoline (271a) with toluene-4-sulphonyl chloride (2.10g, 0.011 mol) in pyridine for 48h was filtered to give a colourless salt (0.10g) which was dissolved in water, basified with solid sodium bicarbonate and extracted with a large volume of chloroform to give a yellow solid, identical (m.p. and i.r. spectrum) to the yellow solid obtained in (ii) above. The pyridine solution was evaporated and the residue was dissolved in chloroform and washed with dilute aqueous sulphuric acid and dilute aqueous sodium hydroxide to give an insoluble brown solid (0.63g) which on stirring with dilute aqueous hydrochloric acid gave 6-chloro-3-hydroxy-2-methyl-1-(toluene-4'-sulphonyl)quinolin-4(1H)-one (286), (0.50g, 28%), identical (m.p. and i.r. spectrum) to an authentic sample prepared as described in (i) above.

The chloroform extract gave a deep red oil (0.70g) whose t.l.c. in chloroform-methanol over silica showed it to be a multi-component mixture. Acidification of the sodium hydroxide washings and extraction with chloroform gave an intractable gum (0.13g).

9. <u>The Attempted Reaction of the N-Hydroxyquinolinone (271a) with Toluene-4-sulphonyl Chloride in Pyridine in the Presence of Sodium Cyanide</u>.

A suspension of the N-hydroxyquinolinone (271a) (0.50g, 0.002 mol) and finely powdered sodium cyanide (0.39g, 0.008 mol) in pyridine (10 ml) was treated with stirring at room temperature with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol). The solid dissolved and the solution became pale at first and then gradually darker. After stirring

at room temperature for 24h, the mixture was evaporated and the residue was treated with dilute aqueous sulphuric acid (10 ml) and chloroform (20 ml) to give a colourless solid (0.57g) which was washed with aqueous 2N sodium carbonate to afford the 3-Hydroxyquinoline (286) (0.32g, 44%), identical (m.p. and i.r. spectrum) to a sample prepared as described in 8(i) above. Acidification of the sodium carbonate washings gave the starting N-hydroxyquinoline (271a) (0.23g, 44%), identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the chloroform extract gave a dark brown intractable gum (0.11g).

10. The Attempted Reaction of the N-Hydroxyquinolinone (271a) with Toluene-4-sulphonyl Chloride in the Presence of Triethylamine.

(i) The N-hydroxyquinolinone (271a) (0.50g, 0.002 mol) and triethylamine (0.35 ml, 0.0025 mol) in dry dimethylformamide (24 ml) was treated dropwise with stirring at room temperature with a solution of toluene-4-sulphonyl chloride in dry dimethylformamide (1.0 ml). The solution became red and stirring was continued for 20 min. The solution was concentrated under reduced pressure, treated with water (15 ml) and extracted with chloroform. The chloroform extract was washed with dilute aqueous sodium hydroxide solution and evaporated to give a brown solid (0.35g), whose t.l.c. in chloroform-methanol over silica showed it to be at least a four component mixture. Acidification of the sodium hydroxide washings and extraction with chloroform gave a brown solid (0.20g), whose t.l.c. (as before) showed it to be an unresolvable three component mixture.

(ii) A solution of the N-hydroxyquinolinone (271a) (0.60g, 0.0024 mol) and triethylamine (0.42 ml, 0.003 mol) in dry dimethylformamide (50 ml) was cooled to -40° (chlorobenzene-dry ice bath) and treated with stirring with toluene-4-sulphonyl chloride (0.52g, 0.0027 mol). After stirring at -40° for 5 min., methanol (100 ml)

was added and the solution was allowed to reach room temperature. Evaporation of the solvents and treatment with water (5.0 ml) gave a pinkish solid (0.72g), which on crystallisation from aqueous dimethylformamide gave the 3-hydroxyquinolinone (286),(0.62g, 71%), identical (m.p. and i.r. spectrum) with a sample prepared as described in 8(i) above. Extraction of the original aqueous mother liquors with chloroform gave a yellow oil which on trituration with methanol gave the starting material (271a), (0.05g, 8%), identical (m.p. and i.r. spectrum) to an authentic sample.

11. The Reaction of the N-Hydroxyquinolinone (271a) with Toluene-4-sulphonyl Chloride in Dimethylformamide.

The N-hydroxyquinolinone (271a) (0.50g, 0.002 mol) was heated under reflux with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol) in dry dimethylformamide (5.0 ml) for 1.5h. Dilution of the black solution with water and extraction with chloroform gave a brown oil which on trituration with ether-chloroform gave a brown solid (0.25g). Crystallisation of this solid from ethanol-dimethylformamide gave 6-chloro-3-hydroxy-2-methylquinolin-4(1H)-one (289b) (0.14g, 33%), m.p. 310-315° (decomp.) [lit.,[207] 320° (decomp.)], identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the ether-chloroform mother liquors gave an intractable brown gum (0.33g).

12. The Attempted Acetylation of the 3-Hydroxyquinolinone (286).

A suspension of the 3-hydroxyquinolinone (286) (0.72g, 0.002 mol) in acetic anhydride (2.0 ml) and concentrated sulphuric acid (0.1 ml) was warmed gently for a few minutes until the solid dissolved. The solution was cooled, poured onto water (10 ml) and the mixture scratched to give the starting material (286) (0.65g, 90%), identical (m.p. and i.r. spectrum) to an authentic sample.

13. The Methylation of the 3-Hydroxyquinolinone (286).

(i) The 3-hydroxyquinolinone (286) (0.72g, 0.002 mol) in 10% w/v aqueous sodium hydroxide (7.5 ml) and water (12.5 ml) was heated to form the sodium salt, treated with dimethyl sulphate (1.0 ml, 0.01 mol) and shaken at room temperature for 1½h to give a colourless solid which was combined with a second crop (total 0.71g) obtained by acidification of the aqueous filtrate to give a quantitative recovery of the starting material (286), identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) The 3-hydroxyquinolinone (286) (1.08g, 0.003 mol) in dry dimethylformamide (50 ml) was treated dropwise with stirring at room temperature with a solution of sodium hydride (0.08g, 0.003 mol) in dry dimethylformamide (1.0 ml). After stirring at room temperature for 15 min., methyl iodide (0.21 ml, 0.0033 mol) was added and stirring was continued for 17h. Dilution of the dark solution with water (100 ml) gave a brown solid (0.40g) which on crystallisation from ethanol-dimethylformamide gave 6-chloro-3-methoxy-2-methyl-1-(toluene-4'-sulphonyl)quinolin-4(1H)-one (290), (0.20g, 18%), as colourless prisms, m.p. 227-228° (decomp.), $\nu_{max.}$ 1625 (CO) cm^{-1}, τ (CF_3CO_2H) 1.45 (1H, m, H-5), 1.85 (2H, m, ArH), 2.02 (2H, d, J_{ortho} 8 Hz, ArH), 2.44 (2H, d, J_{ortho} 8 Hz, ArH), 5.62 (3H, s, OMe), 7.16 (3H, s, ArMe) and 7.43 (3H, s, ArMe).

Found: C,56.8%; H,4.5%; N,3.6%; M^+ 377.

$C_{18}H_{16}ClNO_4S$ requires: C,57.2%; H,4.3%; N,3.7%; M 377.

Extraction of the aqueous mother liquors with chloroform and trituration of the residual gum with chloroform gave starting material (0.07g, 7%), identical (i.r. spectrum) to an authentic sample. Evaporation of the chloroform mother liquors gave a black intractable gum (2.37g).

14. The Attempted Oxidation of the 3-Hydroxyquinolinone (286).

The 3-hydroxyquinoline (286) (0.72g, 0.002 mol) was heated under reflux with a mixture of glacial acetic acid (8.0 ml), water (1.0 ml) and concentrated sulphuric acid (0.5 ml) and treated dropwise with a solution of sodium dichromate (0.60g, 0.0022 mol) in water (1.5 ml). The solution became green and a colourless solid was precipitated. Heating was continued for 24h. The mixture was cooled and diluted with water (15 ml) to give the starting material (286) (0.54g, 75%), identical (m.p. and i.r. spectrum) to an authentic sample. Extraction of the aqueous mother liquors with chloroform gave a negligible quantity of a red gum.

15. The Attempted Alkaline Hydrolysis of the 3-Hydroxyquinolinone (286).

(i) A solution of the 3-hydroxyquinoline (286) (0.36g, 0.001 mol) in 20% w/v aqueous potassium hydroxide (2.5 ml) was heated under reflux for 1h and cooled to give the unreacted starting material (286) (0.09g, 25%), identical (i.r. spectrum) to an authentic sample. Dilution of the filtrate with water gave an intractable solid (0.02g). Acidification of the aqueous mother liquors and extraction with chloroform gave a yellow gum (0.11g) from which no identifiable material could be obtained.

(ii) A solution of the 3-hydroxyquinoline (286) (0.72g, 0.002 mol) and potassium hydroxide pellets (0.24g, 0.0043 mol) in triethylene glycol (10 ml) and water (0.1 ml) was heated under reflux for 0.5h. Dilution of the mixture with water and extraction with chloroform gave a dark red oil whose t.l.c. in chloroform-methanol over silica showed it to be a multi-component mixture. Acidification of the aqueous mother liquors and extraction with chloroform gave a red oil whose t.l.c. (as before) showed it to be a multi-component mixture.

16. The Reaction of the 3-Hydroxyquinolinone (286) with Sodium in Liquid Ammonia.

A suspension of the 3-hydroxyquinolinone (286) (0.72g, 0.002 mol) in liquid ammonia (25 ml) was cooled in an acetone-dry ice bath and treated over a period of 1h with stirring with pieces of sodium (total 0.35g, 0.015 mol) until the blue colour persisted for 10-15 min. The ammonia was allowed to evaporate at room temperature and the residue was treated with water. Acidification of the resulting solution gave a brown solid (0.30g) which on crystallisation (with charcoaling) from ethanol gave 3-hydroxy-2-methylquinolin-4(1H)-one (289a) (0.18g, 50%), m.p. 288-294° (decomp.) [lit.,[207] 297° (decomp.)], identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample. The aqueous mother liquors were extracted with chloroform to give a red oil (0.09g) which was shown by t.l.c. in chloroform-methanol to be a multi-component mixture.

PART 2

1-Hydroxyquinazoline-2(1H),4(3H)-diones

1. The Preparation of Substituted Aminoacetonitriles.

(i) Anilinoacetonitrile was prepared by the reaction of aniline with formaldehyde in the presence of potassium cyanide as described by Knoevenagel[212] (75%) and had m.p. 37-42° (lit.,[212] 48°).

(ii) The hydrochloride of N-benzylaminoacetonitrile was prepared similarly from benzylamine, formaldehyde and potassium cyanide using the method of Baker, Ollis and Poole[211] (70%) and had m.p. 161-167° (lit.,[211] 171°).

2. The Preparation of 5-Chloro-2-nitrobenzoic Acid.

3-Chlorobenzoic acid (40g, 0.255 mol) was added in portions to fuming nitric acid (320 ml) with stirring at room temperature. After stirring for 40 min., the dark solution was poured into water (3 ℓ) at 50° and cooled to 20°. Extraction with ether gave a brown, fuming liquid which was poured into water (750 ml) to give an oil which solidified on rubbing. Crystallisation from benzene-light petroleum with hot filtration to remove unreacted starting material (2.0g) gave 5-chloro-2-nitrobenzoic acid (33.3g, 65%), m.p. 128-134° (lit.,[234] 138°).

3. The Preparation of 2-Nitrobenzoyl Chlorides.

(i) 5-Chloro-2-nitrobenzoyl chloride was prepared from 5-chloro-2-nitrobenzoic acid and phosphorous pentachloride by the method of Montagne[213] (78%) and had b.p. 102-105°/0.5 mm Hg (lit.,[213] 167°/17.0 mm Hg).

(ii) 3-Methyl-2-nitrobenzoyl chloride[214] was similarly prepared (99%) from 3-methyl-2-nitrobenzoic acid and phosphorous pentachloride and had m.p. 72-75°.

4. The Preparation of the N,N-Disubstituted-2'-nitrobenzamides (310 a-d) and (323).

(i) N-Cyanomethyl-N-methyl-2'-nitrobenzamide (310a) was prepared from 2-nitrobenzoyl chloride and N-methylaminoacetonitrile hydrochloride by the method of Spence and Tennant[210] (86%) and had m.p. 103-110° (lit.,[210] 113°).

(ii) N-Benzyl-N-cyanomethyl-2'-nitrobenzamide (310b) was prepared from 2-nitrobenzoyl chloride and N-benzylaminoacetonitrile hydrochloride by the method of Spence and Tennant[210] (79%) and had m.p. 102-109° (lit.,[210] 113°).

(iii) N-Cyanomethyl-N-phenyl-2'-nitrobenzamide (310c) was prepared from 2-nitrobenzoyl chloride and anilinoacetonitrile by the method of Spence and Tennant[210] (67%) and had m.p. 90-95° (lit.,[210] 101°).

(iv) 5-Chloro-2-nitrobenzoyl chloride (4.5g, 0.02 mol) was added dropwise with stirring at room temperature to a slurry of anilinoacetonitrile (2.7g, 0.02 mol) and anhydrous potassium carbonate (5.5g, 0.04 mol) in sodium-dried benzene (45 ml) and the mixture was stirred for 2h. Evaporation of the mixture, treatment with water (25 ml) and extraction with chloroform gave a cream solid (6.3g) which on crystallisation from ethanol-light petroleum gave N-cyanomethyl-N-phenyl-5-chloro-2-nitrobenzamide (310d) (4.9g, 73%), as colourless needles, m.p. 127-129°, $\nu_{max.}$ 1665 (CO) and 1540 and 1350 (NO_2) cm^{-1}, τ [$(CD_3)_2SO$] 1.99 (1H, d, J_{ortho} 9 Hz, H-3'), 2.23 (1H, d, J_{meta} 2 Hz, H-6'), 2.42 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-4'), 2.57-2.82 (5H, m, ArH) and 5.00 (2H, s, CH_2).

Found: C,57.2%; H,3.2%; N,13.5%; M^+315.

$C_{15}H_{10}ClN_3O_3$ requires: C,57.1%; H,3.2%; N,13.3%; M 315.

(v) 3-Methyl-2-nitrobenzoylchloride (5.0g, 0.025 mol) was added in portions with stirring to a slurry of fused sodium acetate (9.4g) and N-methylaminoacetonitrile hydrochloride (2.7g, 0.025 mol) in glacial acetic acid (55 ml) and the mixture was stirred at room temperature for 3h. Evaporation of the mixture, treatment with water (50 ml) and neutralisation with saturated aqueous sodium bicarbonate solution (10 ml) gave N-cyanomethyl-N,3-dimethyl-2-nitrobenzamide (323) (5.6g, 96%), as colourless plates, m.p. 99-100° (from ethanol), $\nu_{max.}$ 1650 (CO) and 1535 and 1355 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.38-2.83 (3H, m, ArH), 5.53 (2H, s, CH_2), 6.94 (3H, s, NMe) and 7.52 (3H, s, ArMe).

Found: C,56.6%; H,4.7%; N,18.0%; M^+ 233.

$C_{11}C_{11}N_3O_3$ requires: C,56.7%; H,4.7%; N,18.0%; M 233.

5. The Preparation of the N-Hydroxyquinazolines (311 a-d) and (324).

(i) The nitrobenzamide (310a) was cyclised in ethanolic sodium ethoxide by the method of Spence and Tennant[210] to give 1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (311a) (90%), m.p. 241-243° (lit.,[210] 245°).

(ii) The nitrobenzamide (310b) was cyclised in ethanolic sodium ethoxide by the method of Spence and Tennant[210] to give 3-benzyl-1-hydroxyquinazoline-2(1H),4(3H)-dione (311b) (83%), m.p. 235-237° (lit.,[210] 237°).

(iii) The nitrobenzamide (310c) was cyclised in ethanolic sodium ethoxide by the method of Spence and Tennant[210] to give 1-hydroxy-3-phenylquinazoline-2(1H),4(3H)-dione (311c) (78%), m.p. 170-179° (lit.,[210] 180°).

(iv) The 2-nitrobenzamide (310d) (0.64g, 0.002 mol) in absolute ethanol (5.0 ml) was treated with a solution of sodium (0.18g, 0.008 mol) in absolute ethanol (5.0 ml) and heated under reflux for 45 min.

Evaporation of the solution under reduced pressure and trituration of the residue with water (4.0 ml) gave a yellow salt (0.40g) which on acidification and extraction with chloroform gave 6-chloro-1-hydroxy-3-phenylquinazoline-2(1H),4(3H)-dione (311d) (0.34g, 59%), as a pale brown solid, m.p. 206-213° (decomp.). Crystallisation from ethanol gave the pure 1-hydroxyquinazoline (311d) as colourless needles, m.p. 219-220° (decomp.), $\nu_{max.}$ 3250-2600 (OH) and 1720, 1665 and 1645 (CO) cm^{-1}.

Found: C,58.3%; H,3.1%; N,9.8%; M^+288.

$C_{14}H_9ClN_2O_3$ requires: C,58.3%; H,3.1%; N,9.7%; M 288.

The original aqueous mother liquors were washed with chloroform to give a red intractable oil (0.10g). Acidification of the aqueous layer and extraction with chloroform gave a red intractable oil (0.22g).

(v) The 2-nitrobenzamide (323) (5.13g, 0.022 mol) in absolute ethanol (55 ml) was treated with a solution of sodium (2.00g, 0.088 mol) in absolute ethanol (55 ml) and heated under reflux for 1h. After removal of the solvent under reduced pressure, the residue was dissolved in water (50 ml), washed with chloroform, acidified and extracted with chloroform to give a brown solid (3.70g) which was crystallised with charcoaling from ethanol to give 1-hydroxy-3,8-dimethylquinazoline-2(1H),4(3H)-dione (324) (2.22g, 50%), as colourless needles, m.p. 181-182°, $\nu_{max.}$ 3100 br (OH) and 1705, 1665 and 1650 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.13 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.50 (1H, 1 dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-7), 2.89 (1H, t, J_{ortho} 8 Hz, H-6), 6.70 (3H, s, NMe) and 7.37 (3H, s, ArMe).

Found: C,58.0%; H,4.9%; N,13.5%; M^+206.

$C_{10}H_{10}N_2O_3$ requires: C,58.3%; H,4.9%; N,13.6%; M 206.

6. The Preparation of 3-Hydroxy-2-phenylquinazolin-4(3H)-one (352).

(i) 2-Aminobenzohydroxamic acid (351) was prepared by the

reaction of methyl anthranilate with hydroxylamine hydrochloride in the presence of sodium hydroxide by the method of Scott and Wood[223] (63%) and had m.p. 143-146° (lit.,[223] 149°).

(ii) 3-Hydroxy-2-phenylquinazolin-4(3H)-one (352) was prepared from 2-aminobenzohydroxamic acid (351) and benzoyl chloride by the method of Schapira and Lamdan[222] (58%) and had m.p. 170-176° (lit.,[222] 177°).

7. The Preparation of 6-Chloro-3-phenylquinazoline-2(1H),4(3H)-dione (339b).

6-Chloro-1-hydroxy-3-phenylquinazolinedione (311d) (0.58g, 0.002 mol) in 70% ethanol (50 ml) was heated under reflux for 1h with sodium dithionite (1.16g) (added in two portions, the second portion after 0.5h). Evaporation of the solvent under reduced pressure and treatment of the residue with water (15 ml) gave a colourless solid (0.53g) which on crystallisation from ethanol afforded 6-chloro-3-phenylquinazoline-2(1H),4(3H)-dione (339b) (0.44g, 80%), as colourless prisms, m.p. 312-313°, $\nu_{max.}$ 3200 (NH) and 1735 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.17 (1H, d, J_{meta} 2 Hz, H-5), 2.29 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-7) and 2.47-2.84 (6H, m, ArH).

Found: C,61.6%; H,3.3%; N,10.5%; M^+272.

$C_{14}H_9ClN_2O_2$ requires: C,61.7%; H,3.3%; N,10.3%; M 272.

8. The Methylation of the Quinazolinediones (339 a and b).

The quinazolinediones (339 a and b) (0.001 mol) in 10% w/v aqueous sodium hydroxide solution (2.5 ml) were treated with dimethyl sulphate (0.5 ml, 0.0052 mol) and shaken at room temperature for 17h to give a colourless solid which on crystallisation from ethanol-glacial acetic acid gave the pure methylated product.

(i) The quinazolinedione (339a) gave 1-methyl-3-phenyl-

quinazoline-2(1H),4(3H)-dione (339c) (0.21g, 75%), as colourless prisms, m.p. 231-232°, $\nu_{max.}$ 1710, 1680 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 1.95 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.19 (1H, m, ArH), 2.44-2.80 (7H, m, ArH) and 6.50 (3H, s, NMe).

Found: C,71.3%; H,4.9%; N,11.0%; M^+252.

$C_{15}H_{12}N_2O_2$ requires: C,71.4%; H,4.8%; N,11.1%; M 252.

(ii) The quinazolinedione (339b) gave 6-chloro-1-methyl-3-phenylquinazoline-2(1H),4(3H)-dione (339d) (0.21g, 75%), as colourless needles, m.p. 237-238°, $\nu_{max.}$ 1710 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.05 (1H, d, J_{meta} 2 Hz, H-5), 2.17 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-7), 2.40-2.81 (6H, m, ArH) and 6.49 (3H, s, NMe).

Found: C,63.1%; H,4.1%; N,9.9%; M^+286.

$C_{15}H_{11}ClN_2O_2$ requires: C,62.8%; H,3.9%; N,9.8%; M 286.

9. The Prolonged Reaction of the N-Hydroxyquinazoline (311b) with Acetic Anhydride.

The N-hydroxyquinazoline (311b) (0.14g, 0.0005 mol) in acetic anhydride (2.0 ml) was heated at 100° for 4h. Evaporation of the mixture and trituration with ether gave 1-acetoxy-3-benzylquinazoline-2(1H),4(3H)-dione (312b) (0.15g, 93%), which had m.p. 145-149° (lit.,[210] 151°), identical (m.p. and i.r. spectrum) to an authentic sample.

10. The Reaction of the N-Hydroxyquinazoline (311c) with Toluene-4-sulphonyl Chloride in Dimethylformamide.

The N-hydroxy compound (311c) (0.50g, 0.002 mol) in dry dimethylformamide (2.5 ml) was heated with toluene-4-sulphonyl chloride at 100° for 1h. Evaporation of the solvent and treatment of the residue with water (5.0 ml) gave a pale brown solid (0.52g) whose t.l.c. in chloroform-methanol over silica showed it to be a multi-component mixture, which was not investigated further.

11. The Reactions of the N-Hydroxyquinazolines (311 a-d) and (324) with Sulphonyl Halides in the Presence of Triethylamine.

The N-hydroxyquinazolines (311 a-d) and (324) (0.002 mol) and triethylamine (0.35 ml, 0.0025 mol) in dry dioxan were treated dropwise with stirring at room temperature with a solution of the sulphonyl halide (0.0022 mol) in dry dioxan (1.0 ml) and the mixture was stirred for 15 min. The initial pale yellow colour disappeared and a colourless precipitate of triethylamine hydrochloride appeared, m.p. 245-249° (lit.,[235] 254°). Evaporation of the solvent and treatment with water (10 ml) gave the product which was pure enough to be used in further transformations. The N-sulphonyloxy products were crystallised only once for analysis since prolonged heating in organic solvents caused rearrangement.

(i) The reaction of the N-hydroxy compound (311a) in dry dioxan (24 ml) with toluene-4-sulphonyl chloride (0.42g) gave 3-methyl-1-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (313a) (91%), as colourless needles, m.p. 120-121° (with resolidification and further melting at 170-195°) (from ethanol-tetrahydrofuran), $\nu_{max.}$ 1725 and 1685 (CO) cm^{-1}, τ ($CDCl_3$) 1.86 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.01 (2H, d, J_{ortho} 8 Hz, ArH), 2.22-2.85 (5H, m, ArH), 6.53 (3H, s, NMe) and 7.52 (3H, s, ArMe).

Found: C,55.4%; H,4.1%; N,8.0%; M^+346.

$C_{16}H_{14}N_2O_5S$ requires: C,55.5%; H,4.1%; N,8.1%; M 346.

(ii) The reaction of the N-hydroxy compound (311b) (0.54g) in dry dioxan (14 ml) with toluene-4-sulphonyl chloride (0.42g) gave 3-benzyl-1-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (313b) (90%), as colourless prisms, m.p. 115-116° (with resolidification and further melting at 185-193°) (from ethanol-tetrahydrofuran), $\nu_{max.}$ 1740 and 1685 (CO) cm^{-1}, τ ($CDCl_3$) 1.87 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.09 (2H, d, J_{ortho} 8 Hz, ArH), 2.23-2.58 (3H, m, ArH), 2.58-2.85 (7H, m, ArH), 4.89 (2H, s, CH_2) and 7.54 (3H, s, ArMe).

Found: C,62.3%; H,4.4%; N,6.8%; M^+422.

$C_{22}H_{18}N_2O_5S$ requires: C,62.6%; H,4.3%; N,6.6%; M 422.

(iii) The reaction of the N-hydroxy compound (311c) (0.50g) in dry dioxan (10 ml) with toluene-4-sulphonyl chloride (0.42g) gave 3-phenyl-1-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (313c) (95%), as colourless needles, m.p. 132-134° (with resolidification and further melting at 170-190°) (from acetone), $\nu_{max.}$ 1730 and 1695 (CO) cm^{-1}, τ ($CDCl_3$) 1.81 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.01 (2H, d, J_{ortho} 8 Hz, ArH), 2.13-2.92 (10H, m, ArH) and 7.56 (3H, s, ArMe).

Found: C,61.7%; H,4.0%; N,7.1%; M^+408.

$C_{21}H_{16}N_2O_5S$ requires: C,61.8%; H,4.0%; N,6.9%; M 408.

(iv) The reaction of the N-hydroxy compound (311a) (0.40g) in dry dioxan (24 ml) with methanesulphonyl chloride (0.20 ml, 0.0026 mol) gave, after washing with saturated aqueous sodium bicarbonate solution (5.0 ml) and water (5.0 ml), 1-(methanesulphonyloxy)-3-methylquinazoline-2(1H),4(3H)-dione (311d) (70%; 83% based on unrecovered starting material), as colourless prisms, which sublimed at 122-123° with rearrangement and subsequent melting at 249-269° (from methanol-acetone), $\nu_{max.}$ 1725 and 1680 (CO) cm^{-1}, τ ($CDCl_3$) 1.85 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.18-2.39 (1H, m, ArH), 2.49-2.79 (2H, m, ArH), 6.41 (3H, s, SO_2Me) and 6.54 (3H, s, NMe).

Found: C,44.2%; H,3.7%; N,10.2%; M^+270.

$C_{10}H_{10}N_2O_5S$ requires: C,44.4%; H,3.7%; N,10.4%; M 270.

Acidification of the sodium bicarbonate washings gave starting material (16%), identical (m.p. and i.r. spectrum) to an authentic sample.

(v) The reaction of the N-hydroxy compound (311d) (0.58g) in dry dioxan (20 ml) with toluene-4-sulphonyl chloride (0.42g) gave 6-chloro-3-phenyl-1-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (320) (85%), as colourless prisms, m.p. 129-131° (with resolidification

and further melting at 212-225° (from acetone-methanol), $\nu_{max.}$ 1740 and 1690 (CO) cm^{-1}, τ ($CDCl_3$) 1.90 (1H, d, J_{meta} 2 Hz, H-5), 2.04 (2H, d, J_{ortho} 8 Hz, ArH), 2.25-2.93 (9H, m, ArH) and 7.57 (3H, s, ArMe).

Found: C,56.6%; H,3.4%; N,6.1%; M^+442.

$C_{21}H_{15}ClN_2O_5S$ requires: C,57.0%; H,3.4%; N,6.3%; M 442.

(vi) The reaction of the N-hydroxy compound (324) (0.41g) in dry dioxan (20 ml) with toluene-4-sulphonyl chloride (0.42g) gave, after extraction with chloroform, a yellow oil (0.70g) which on trituration with ether yielded a pale brown solid (0.58g). T.l.c. of the solid and of the trituration liquors in chloroform over silica showed the presence of multi-component mixtures which were not further investigated.

Repetition of the reaction in dry tetrahydrofuran (15 ml) with stirring at -10° for 15 min. gave, after extraction with chloroform and trituration of the resultant oil with ether, a pale brown solid (0.62g) whose t.l.c. in chloroform over silica showed it to be a multi-component mixture, which was not investigated further.

12. The Hydrolysis of the N-(Toluene-4-sulphonyloxy)quinazoline (313a).

A suspension of the quinazoline (313a) (0.70g, 0.002 mol) in 5% w/v aqueous sodium hydroxide was stirred at 50° for 1h. The insoluble starting material was collected (0.48g, 70%) and identified by comparison (m.p. and i.r. spectrum) with an authentic sample. Acidification of the filtrate gave 1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (311a) (0.09g, 25%; 83% based on unrecovered starting material), identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample.

13. The Thermal Rearrangement of the N-Sulphonyloxyquinazolines (313 a-d) and (320).

The N-sulphonyloxyquinazolines (313 a-d) and (320) (0.001 mol) were heated in a cold finger sublimation apparatus under reduced pressure (water

pump) at their melting points (oil bath) for 20 min. After cooling, the glassy solids (which were shown by t.l.c. in ether over activity III alumina to be two component mixtures) were collected and separated into their components by preparative t.l.c. in ether over silica.

(i) The N-(toluene-4-sulphonyloxy)quinazoline (313a) (0.35g), heated at 110°, gave a pale brown solid (0.34g). Separation by preparative t.l.c. gave as the faster-moving component 3-methyl-8-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (314a) (0.24g, 75%), colourless prisms, m.p. 209-210° (from ethanol-dioxan), $\nu_{max.}$ 3300-2800 (NH) and 1715 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.07-2.27 (3H, m, ArH), 2.48-2.66 (3H, m, ArH), 2.85 (1H, t, J_{ortho} 8 Hz, H-6), 6.80 (3H, s, NMe) and 7.62 (3H, s, ArMe),

Found: C,55.6%; H,4.2%; N,8.2%; M^+346.

$C_{16}H_{14}N_2O_5S$ requires: C,55.5%; H,4.1%; N,8.1%; M 346.

and as the slower-moving component 3-methyl-6-(toluene-4-sulphonyloxy)-quinazoline-2(1H),4(3H)-dione (315a) (0.07g, 20%), colourless plates, m.p. 219-220° (from ethanol), $\nu_{max.}$ 3200 (NH) and 1725 and 1650 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.26 (2H, d, J_{ortho} 8 Hz, ArH), 2.44-2.66 (3H, m, ArH), 2.70-2.91 (2H, m, ArH), 6.79 (3H, s, NMe) and 7.58 (3H, s, ArMe).

Found: C,55.1%; H,4.2%; N,8.0%; M^+346.

$C_{16}H_{14}N_2O_5S$ requires: C,55.5%; H,4.1%; N,8.1%; M 346.

(ii) The N-(toluene-4-sulphonyloxy)quinazoline (313b) (0.42g), heated at 105°, gave a pale brown solid (0.39g). Separation by preparative t.l.c. gave as the faster-moving component 3-benzyl-8-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (314b) (0.30g, 73%), as colourless needles, m.p. 199-200° (from ethanol-tetrahydrofuran), $\nu_{max.}$ 3200 (NH) and 1710 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.06-2.31 (3H, m, ArH), 2.39-2.92 (9H, m, ArH), 4.98 (2H, s, CH_2) and 7.69 (3H, s, ArMe),

Found: C,62.0%; H,4.4%; N,6.5%; M^+422.

$C_{22}H_{18}N_2O_5S$ requires: C,62.5%; H,4.3%; N,6.6%; M 422.

and as the slower moving component 3-benzyl-6-(toluene-4-sulphonyloxy)-

quinazoline-2(1H),4(3H)-dione (315b) (0.07g, 16%), as colourless plates, m.p. 223-224° (from ethanol), $\nu_{max.}$ 3300 (NH) and 1720 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.18-2.32 (2H, m, ArH), 2.44-2.66 (10H, m, ArH), 4.95 (2H, s, CH_2) and 7.58 (3H, s, ArMe).

Found: C,62.0%; H,4.5%; N,6.6%; M^+422.

$C_{22}H_{18}N_2O_5S$ requires: C,62.5%; H,4.3%; N,6.6%; M 422.

(iii) The N-(toluene-4-sulphonyloxy)quinazoline (313c) (0.40g), heated at 130°, gave a pale brown solid (0.39g). Separation by preparative t.l.c. gave as the faster-moving component 3-phenyl-8-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (314c) (0.26g, 65%), as colourless prisms, m.p. 202-203° (from acetone-ethanol), $\nu_{max.}$ 3300 (NH) and 1725 and 1690 (CO) cm^{-1}, τ (CF_3CO_2H) 1.81 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.11 (2H, d, J_{ortho} 8 Hz, ArH), 2.34-2.79 (9H, m, ArH) and 7.51 (3H, s, ArMe),

Found: C,61.8%; H,3.9%; N,7.0%; M^+408.

$C_{21}H_{16}N_2O_5S$ requires: C,61.8%; H,4.0%; N,6.9%; M 408.

and as the slower-moving component 3-phenyl-6-(toluene-4-sulphonyloxy)-quinazoline-2(1H),4(3H)-dione (315c) (0.12g, 30%), as colourless prisms, m.p. 215-216° (from ethanol), $\nu_{max.}$ 3100-2600 (NH) and 1725 and 1680 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.06-2.31 (3H, m, ArH), 2.38-2.86 (9H, m, ArH) and 7.58 (3H, s, ArMe).

Found: C,61.9%; H,4.1%; N,6.7%; M^+408.

$C_{21}H_{16}N_2O_5S$ requires: C,61.8%; H,4.0%; N,6.9%; M 408.

(iv) The N-methanesulphonyloxyquinazoline (313d) (0.27g), heated at 110°, gave a pale brown solid (0.26g). Separation by preparative t.l.c. gave as the faster-moving component 8-methanesulphonyloxy-3-methylquinazoline-2(1H),4(3H)-dione (314d) (0.21g, 77%), as colourless needles, m.p. 272-273° (from dimethylformamide), $\nu_{max.}$ 3150 (NH) and 1705 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.09 (1H, dd, J_{ortho} 8 Hz, J_{meta}

2 Hz, H-5), 2.36 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-7), 2.78 (1H, t, J_{ortho} 8 Hz, H-6), 6.43 (3H, s, SO_2Me) and 6.74 (3H, s, NMe),

Found: C,44.8%; H,3.8%; N,10.5%; M^+270.

$C_{10}H_{10}N_2O_5S$ requires: C,44.4%; H,3.7%; N,10.4%; M 270.

and as the slower-moving component 6-methanesulphonyloxy-3-methylquinazoline-2(1H),4(3H)-dione (315d) (0.04g, 15%), as colourless needles, m.p. 261-262° (from dimethylformamide), $\nu_{max.}$ 3150 (NH) and 1725 and 1650 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.18 (1H, d, J_{meta} 3 Hz, H-5), 2.36 (1H, dd, J_{ortho} 9 Hz, J_{meta} 3 Hz, H-7), 2.69 (1H, d, J_{ortho} 9 Hz, H-8), 6.61 (3H, s, SO_2Me) and 6.74 (3H, s, NMe).

Found: C,44.4%; H,3.8%; N,10.3%; M^+270.

$C_{10}H_{10}N_2O_5S$ requires: C,44.4%; H,3.7%; N,10.4%; M 270.

(v) The N-(toluene-4-sulphonyloxy)quinazoline (320) (0.44g), heated at 100°, gave a pale brown solid (0.42g). T.l.c. in chloroform-methanol over silica showed one major component and traces of several minor components. Crystallisation from aqueous dioxan gave 6-chloro-3-phenyl-8-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (321) (0.32g, 73%), as colourless needles, m.p. 231-232°, $\nu_{max.}$ 3100-2600 (NH) and 1730 and 1685 (CO) cm^{-1}, τ ($CDCl_3$) 1.58 (1H, br, s, NH), 2.01 (1H), d, J_{meta} 2 Hz, H-5), 2.19 (2H, d, J_{ortho} 8 Hz, ArH), 2.43-2.85 (8H, m, ArH) and 7.52 (3H, s, ArMe).

Found: C,56.8%; H,3.9%; N,5.9%; M^+442.

$C_{21}H_{15}ClN_2O_5S$ requires: C,57.0%; H,3.4%; N,6.3%; M 442.

Evaporation of the crystallisation mother liquors gave a brown solid (0.09g) whose t.l.c. in chloroform-methanol over silica showed it to be an unresolvable multi-component mixture.

14. The Thermal Rearrangement of the N-(Toluene-4-sulphonyloxy)-quinazoline (313a) in Solution.

The quinazoline (313a) (0.35g, 0.001 mol) was heated under reflux in glacial acetic acid (5.0 ml) or dry tetrahydrofuran (6.0 ml) for

1 - 1.75h. Evaporation of the solution and treatment of the residue with water (5.0 ml) gave a colourless solid (0.30-0.35g) which was shown by t.l.c. in chloroform over silica to be identical to the mixture of (314a) and (315a) formed by thermal rearrangement of (313a) in the absence of solvent [cf. 13(i)], except for a trace of a third, slower moving component. The i.r. spectrum of the mixture was identical to that of the sample obtained before.

15. The Attempted Hydrolysis of the 8-(Toluene-4-sulphonyloxy)-quinazoline (314c)

The quinazoline (314c) (0.41g, 0.001 mol) in 0.5 N aqueous sodium hydroxide solution (40 ml) was heated under reflux for 4h. After cooling and washing with chloroform, the aqueous layer was acidified and extracted with chloroform to give an intractable red oil (0.07g). The aqueous layer was neutralised with sodium acetate and subjected to constant chloroform extraction for 16h to give a dark intractable solid (0.09g) which was not further investigated.

16. The Methylation of the 8-(Toluene-4-sulphonyloxy)quinazoline (314c)

The quinazoline (314c) (0.82g, 0.002 mol) in anhydrous acetone (60 ml) was treated with anhydrous potassium carbonate (2.13g) and dimethyl sulphate (1.2 ml, 0.0125 mol) and the mixture was heated under reflux for 4h. Hot filtration removed inorganic solid which was dissolved in water (10 ml) and extracted with chloroform to give a brown gum (0.15g). The gum was combined with the solid (0.65g), obtained by evaporating the acetone filtrate, and treated with water (10 ml), and crystallised from ethanol-acetic acid to give 1-methyl-3-phenyl-8-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (319) (0.52g, 62%), as colourless prisms, m.p. 215-217°, $\nu_{max.}$ 1715 and 1675 (CO) cm^{-1}, τ ($CDCl_3$) 1.85 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.32 (2H, d, J_{ortho} 8 Hz, ArH), 2.46-2.90 (9H, m, ArH), 6.32 (3H, s, NMe)

and 7.54 (3H, s, ArMe).

Found: C,62.8%; H,4.4%; N,6.6%; M^+422.

$C_{22}H_{18}N_2O_5S$ requires: C,62.6%; H,4.3%; N,6.6%; M 422.

Concentration of the crystallisation liquors gave a colourless solid (0.10g) whose ^1H n.m.r. spectrum (60 MHz) showed it to be a mixture consisting mainly of the N-methylquinazoline (319) plus a relatively small amount of another component (peak at τ 6.17).

17. The Preparation of 8-Methoxy-1-methyl-3-phenylquinazoline-2(1H),4(3H)-dione (316).

The N-methylquinazoline (319) (0.31g, 0.0007 mol), suspended in 5% aqueous sodium hydroxide solution (3.0 ml), was stirred at 100° for 4h. The solution was cooled, treated with dimethyl sulphate (0.37 ml, 0.004 mol) and shaken for 20h at room temperature. Extraction with chloroform and trituration of the resultant gum with ether gave 8-methoxy-1-methyl-3-phenylquinazoline-2(1H),4(3H)-dione (316) (0.12g, 62%), as colourless needles, m.p. 203-204° (from ethanol), $\nu_{max.}$ 1710 and 1660 (CO) cm^{-1}.

Found: C,68.2%; H,5.1%; N,9.9%; M^+282.

$C_{16}H_{14}N_2O_3$ requires: C,68.1%; H,5.0%; N,9.9%; M 282.

18. The Unambiguous Synthesis of the 8-Methoxy-1-methylquinazoline (316).

(i) A solution of 3-hydroxyanthranilic acid (317) (0.10g, 0.0075 mol) in dry dimethylformamide (0.5 ml) was treated with phenyl isocyanate (0.17 ml, 0.0015 mol) and left at room temperature for 16h. Treatment with water (3.0 ml) gave a pinkish solid (0.18g) which on crystallisation from ethanol-light petroleum afforded 8-hydroxy-3-phenylquinazoline-2(1H),4(3H)-dione (318) (0.10g, 60%), as pinkish prisms, m.p. 283-287° (decomp.), $\nu_{max.}$ 3450 and 3280 (OH) and 1740 and 1640 (CO) cm^{-1}.

Found: C,66.3%; H,4.1%; N,11.1%; M^+254.

$C_{14}H_{10}N_2O_3$ requires: C,66.1%; H,4.0%; N,11.0%; M 254.

(ii) The 8-hydroxy compound (318) (0.05g, 0.0002 mol) in 10% w/v aqueous sodium hydroxide (1.0 ml) was shaken with dimethyl sulphate (0.2 ml, 0.002 mol) at room temperature for 15h. Extraction with chloroform and trituration of the residue with ether gave 8-methoxy-1-methyl-3-phenylquinazoline-2(1H),4(3H)-dione (316) (0.03g, 54%), identical (m.p., mixed m.p. and i.r. spectrum) to the sample obtained as described previously in 17.

19. The Attempted Rearrangement of the 8-Sulphonyloxyquinazoline (314a).

The quinazoline (314a) was heated at 140° for 0.5h. The solid did not melt and on cooling was shown (m.p., i.r. spectrum and t.l.c. in chloroform-methanol over silica) to be identical with the starting material.

20. The Reaction of the N-Sulphonyloxyquinazoline (313a) with Lithium Chloride in Glacial Acetic Acid.

A solution of the quinazoline (313a) (0.35g, 0.001 mol) and lithium chloride (0.17g, 0.004 mol) in glacial acetic acid (25 ml) was stirred at 40° for 26h. Evaporation of the solution and treatment of the residue with water (5.0 ml) gave a colourless solid (0.30g) which was identical (t.l.c. in chloroform-methanol over silica and i.r. spectrum) to the mixture of (314a) and (315b) obtained by the thermal rearrangement of (313a) in the absence of solvent [cf. 13(i)].

21. The Reaction of the N-Sulphonyloxyquinazoline (313a) with Sodium Acetate in Glacial Acetic Acid.

The quinazoline (313a) (0.35g, 0.001 mol) and fused sodium acetate (0.33g, 0.004 mol) in glacial acetic acid (25 ml) were stirred at room temperature for 18h. Evaporation of the mixture and treatment of the residue with water (10 ml) gave a colourless solid (0.30g) which was

identical (t.l.c. in chloroform-methanol over silica and i.r. spectrum) to the mixture of (314a) and (315a) obtained by the thermal rearrangement of (313a) in glacial acetic acid (cf. 14). Extraction of the aqueous filtrate with chloroform gave a colourless solid (0.04g) whose t.l.c in chloroform-methanol over silica showed it to be almost identical to the isomer mixture [(314a) and (315a)] with the exception of a component exhibiting yellow fluorescence at 366 nm. The i.r. spectrum of the solid also contained an additional band at 1750 (CO) cm^{-1} and the ^1H n.m.r. spectrum [$(CD_3)_2SO$ - 60 M Hz] contained an additional singlet at τ 8.1.

22. The Attempted Reaction of the N-Sulphonyloxyquinazoline (313a) with Pyrrolidine.

The quinazoline (313a) (0.35g, 0.001 mol) in dry dioxan (10 ml) was stirred with pyrrolidine (0.35 ml, 0.004 mol) at 40° for 24h. Evaporation of the red solution and treatment with dilute aqueous sulphuric acid (5.0 ml) gave a brown solid (0.27g) whose t.l.c. in chloroform-methanol over silica showed it to be mainly the mixture of isomers [(314a) and (315a)] with traces of at least four other components. Extraction of the aqueous filtrate with chloroform gave a red oil (0.03g) whose t.l.c. showed it to be an unresolvable multi-component mixture. Basification of the aqueous mother liquors with sodium bicarbonate and extraction with chloroform likewise gave a multi-component red oil (0.03g).

23. The Reaction of the N-Sulphonyloxyquinazoline (313a) with Sodium Methanesulphonate.

(i) The quinazoline (313a) (0.10g, 0.003 mol) in 70% v/v dimethylformamide - water (10 ml) was stirred at 40° for 24h. Evaporation of solvents and treatment with water (5.0 ml) gave a colourless solid (0.08g)

whose t.l.c. in chloroform-methanol over silica showed it to contain the same three components as the mixture obtained by the thermal rearrangement of (313a) in glacial acetic acid (cf. 14), τ (60 MHz) $[(CD_3)_2SO]$ 2.0-3.1 (17 units, m, ArH), 6.8 (9 units, m, NMe) and 7.6 (8 units, s, ArMe).

(ii) The quinazoline (313a) (0.35g, 0.001 mol) and sodium methanesulphonate (0.47g, 0.004 mol) in 70% v/v dimethylformamide - water (60 ml) were stirred at 40° for 13h. Evaporation of the solvents and treatment with water (5.0 ml) gave a colourless solid (0.27g), identical (i.r. and ^1H n.m.r. spectra and t.l.c. in chloroform-methanol over silica) to the solid obtained as described in (i), above.

24. The Reaction of the N-Hydroxyquinazoline (311c) with Toluene-4-sulphonyl Chloride in Pyridine.

The N-hydroxyquinazoline (311c) (3.75g, 0.015 mol) in pyridine (15 ml) was treated with stirring at room temperature with toluene-4-sulphonyl chloride (3.45g, 0.018 mol) and the mixture was stirred for 72h. The insoluble colourless salt (0.55g) was collected, dissolved in water and the solution was just basified with solid sodium bicarbonate. Evaporation of the solution and crystallisation of the residue from ethanol with a few drops of water gave anhydro 1-(1,3-dihydro-2,4-dioxo-3-phenylquinazolin-6-yl)pyridinium hydroxide (338) (0.37g, 8%), as yellow prisms, which decompose without melting at 200-250°, $\nu_{max.}$ 3400 br (OH) and 1665 (CO) cm^{-1}, τ (CF_3CO_2H) 0.86-1.02 (2H, m, ArH), 1.10-1.41 (2H, m, ArH), 1.59-1.96 (3H, m, ArH), 2.24 (1H, d, J_{ortho} 8 Hz, H-8), 2.31-2.49 (3H, m, ArH) and 2.53-2.72 (2H, m, ArH).

Found: C,62.8%; H,4.2%; N,11.8%; M^+316.

$C_{19}H_{13}N_3O_2$ requires: C,72.4%; H,4.2%; N,13.3%; M 315.

$C_{19}H_{15}N_3O_5$ requires: C,62.5%; H,4.1%; N,11.5%.

Exact Mass: Found: 316.108943 mass units.

$C_{19}H_{14}N_3O_2$ requires: 316.108595 mass units.

Evaporation of the pyridine mother liquors gave a brown oil which was dissolved in chloroform and washed with dilute aqueous hydrochloric acid (15 ml) and dilute aqueous sodium hydroxide solution (15 ml) to give a brown froth which on trituration with a little ether yielded 3-phenyl-8-(toluene-4-sulphonyloxy)quinazoline-2(1H),4(3H)-dione (314c) (2.20g, 36%), identical (m.p. and i.r. spectrum) to the sample obtained by the thermal rearrangement of (313c) [cf. 13 (iii)]. Acidification of the sodium hydroxide washings and extraction with chloroform gave a pink solid (1.22g) which on crystallisation from ethanol gave a colourless solid (1.00g), m.p. 278-283° (decomp.), $\nu_{max.}$ 3200 (NH) and 1735 and 1655 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.08 (4 units, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, ArH), 2.17 (1 unit, d, J_{meta} 2 Hz, ArH), 2.20-2.43 (5 units, m, ArH) and 2.43-2.90 (32 units, m, ArH),

Found: C,66.6%; H,3.8%; N,11.0%; M^+272 and 238.

$C_{14}H_9ClN_2O_2$ requires: C,61.6%; H,3.3%; N,10.3%; M 272.

$C_{14}H_{10}N_2O_2$ requires: C,70.6%; H,4.2%; N,11.8%; M 238.

which was shown to be a 4:1 mixture of 3-phenylquinazoline-2(1H),4(3H)-dione (339a) and 6-chloro-3-phenylquinazoline-2(1H),4(3H)-dione (339b) by comparison (i.r. and ^1H n.m.r. spectra and t.l.c. in chloroform or chloroform-methanol over silica) with an authentic mixture.

The mixture (0.50g, ~0.002 mol) was methylated by shaking with 10% w/v aqueous sodium hydroxide solution (5.0 ml) and dimethyl sulphate (2.0 ml, 0.021 mol) at room temperature for 24h to give a colourless insoluble solid (0.49g), m.p. 192-210° (decomp.), $\nu_{max.}$ 1710, 1680 and 1665 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 1.95 (4 units, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, ArH), 2.04 (1 unit, d, J_{meta} 2 Hz, ArH), 2.09-2.29 (5 units, m, ArH), 2.40-2.79 (30 units, m, ArH) and 6.50 (15 units, s, NMe), which was shown to be an unresolvable 4:1 mixture of 1-methyl-3-phenylquinazoline-

2(1H),4(3H)-dione (339c) and 6-chloro-1-methyl-3-phenylquinazoline-2(1H), 4(3H)-dione (339d) by comparison (m.p., i.r. and ^{1}H n.m.r. spectra and t.l.c. in various solvents over silica or alumina) with an authentic mixture. An attempt to separate the mixture by sublimation was unsuccessful.

25. The Reaction of the N-Hydroxyquinazoline (311a) with 3,5-Dinitrobenzoyl Chloride in Pyridine.

The N-hydroxy compound (311a) (0.40g, 0.002 mol) in pyridine (3.0 ml) was treated with stirring at room temperature with 3,5-dinitrobenzoyl chloride (0.50g, 0.0022 mol) and the mixture was stirred for 10 min. Evaporation of the solvent and trituration of the residue with dilute aqueous sulphuric acid (5.0 ml) gave a colourless solid which was washed with saturated aqueous sodium bicarbonate solution (5.0 ml), followed by water, and crystallised to give 3-methyl-1-(3,5-dinitrobenzoyloxy)-quinazoline-2(1H),4(3H)-dione (344) (0.70g, 90%; quantitative based on unrecovered starting material), as colourless needles, m.p. 205-206° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 1785, 1720 and 1690 (CO) and 1555 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 0.66 (3H, s, ArH), 1.74 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.33 (1H, dt, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-7), 2.66 (1H, dt, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-6), 2.94 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-8) and 6.49 (3H, s, NMe).

Found: C,49.8%; H,2.6%; N,14.6%; M^+386.

$C_{16}H_{10}N_4O_8$ requires: C,49.8%; H,2.6%; N,14.5%; M 386.

Acidification of the sodium bicarbonate washings gave starting material (311a) (0.04g, 10%), identical (m.p. and i.r. spectrum) to an authentic sample.

26. The Attempted Rearrangement of the N-Benzoyloxyquinazoline (344).

The N-benzoyloxyquinazoline (344) (0.19g, 0.005 mol) was heated in

a cold-finger vacuum sublimation apparatus under reduced pressure (water pump) at 180° for 1h. A colourless solid sublimed on to the cold-finger (0.02g) whose t.l.c. in chloroform over silica showed it to be at least a two component mixture which was not investigated further. The residual material was a glassy solid (0.15g) whose t.l.c. in chloroform over silica showed it to be an unresolvable multi-component mixture.

27. The Attempted Reaction of the N-Benzoyloxyquinazoline (344) with Glacial Acetic Acid.

The N-benzoyloxy compound (344) (0.20g, 0.0005 mol) in glacial acetic acid (2.0 ml) was heated under reflux for 1h. Evaporation of the mixture and treatment with saturated aqueous sodium bicarbonate solution (5.0 ml) gave the starting material (344) (0.04g, 20%), identical (i.r. spectrum) to an authentic sample. Acidification of the filtrate gave a colourless solid (0.13g) which on leaching with boiling water and hot filtration gave 1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (311a) (0.08g, 80%; quantitative based on unrecovered starting material), identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the aqueous filtrate gave 3,5-dinitrobenzoic acid (0.04g, 38%; 47% based on unrecovered starting material), identical (i.r. spectrum) to an authentic sample.

28. The Reaction of the N-Hydroxyquinazoline (311a) with Picryl Chloride in the Presence of Triethylamine.

A solution of the N-hydroxy compound (311a) (0.40g, 0.002 mol) and triethylamine (0.35 ml , 0.0025 mol) in dry dioxan (20 ml) was treated with stirring at room temperature with a solution of picryl chloride (containing 20% by weight of water) (0.67g, 0.0022 mol) in dioxan (1.0 ml) and the mixture was stirred at room temperature for 10 min. The red solution was evaporated and the residue was treated with

chloroform. The chloroform extract was washed with dilute aqueous sulphuric acid (5.0 ml) and dilute aqueous sodium hydroxide solution (10 ml) and evaporated to give a dark red oil (0.31g) which was shown by t.l.c. in chloroform-methanol over silica to be an unresolvable multi-component mixture. Acidification of the sodium hydroxide washings gave a brown solid (0.15g) which was shown by t.l.c. (as above) to be a three component mixture. Crystallisation from aqueous ethanol failed to resolve the mixture. Extraction of the acidified mother liquors with chloroform gave a red oil (0.24g) which was shown by t.l.c. (as above) to be an unresolvable multi-component mixture.

29. The Attempted Reaction of the N-Hydroxyquinazoline (311a) with 2,4-Dinitrochlorobenzene in the Presence of Triethylamine.

A solution of the N-hydroxyquinazoline (311a) (0.38g, 0.002 mol) and triethylamine (0.35 ml, 0.0025 mol) in dry dioxan (20 ml) was treated with stirring with a solution of 2,4-dinitrochlorobenzene (0.41g, 0.0022 mol) in dioxan (1.0 ml) and the mixture was stirred for 42h at 40°. More triethylamine (0.35 ml, 0.0025 mol) was added and stirring was continued at 40° for a further 7h. Evaporation of the solution, treatment with water (10 ml) and extraction with chloroform gave an orange oil (1.50g) which on trituration with ether gave the starting material (311a) (0.10g, 26%), identical (i.r. spectrum) to an authentic sample. T.l.c. of the oil, recovered from the mother liquors, in chloroform-methanol over silica showed it to contain an unresolvable mixture of 2,4-dinitrochlorobenzene and two other yellow components.

30. The Reaction of the N-Hydroxyquinazoline (311a) with 2,4-Dinitrochlorobenzene in the Presence of Sodium Ethoxide.

The N-hydroxy compound (311a) (0.38g, 0.002 mol) in absolute ethanol (70 ml) was treated with a solution of sodium (0.05g, 0.0022 mol) in

absolute ethanol (5.0 ml). The resultant suspension was treated with 2,4-dinitrochlorobenzene (0.41g, 0.0022 mol) in absolute ethanol (15 ml) and the mixture was heated under reflux for 1h. The suspended salt had dissolved after 15 min. The yellow solution was evaporated, treated with water (10 ml) and extracted with chloroform to give an orange oil (0.40g) which, on trituration with a little ether, gave an orange solid (0.35g), whose t.l.c. in chloroform-methanol over silica showed it to be a mixture of at least seven components, one of which was the starting material. Crystallisation from ethanol-glacial acetic acid or aqueous acetic acid failed to resolve the mixture. Acidification of the aqueous mother liquors and extraction with chloroform gave a red oil (0.25g) which on trituration with ether gave a yellow solid (0.14g). Crystallisation from glacial acetic acid gave an unidentified solid (0.09g, 12%), as pale yellow needles, m.p. 266-269°, $\nu_{max.}$ 3200 (OH), 1715, 1680 and 1665 (CO) and 1560, 1540, 1355 and 1330 (NO_2) cm^{-1}, τ $[(CD_3)_2SO]$ 1.13 (1H, d, J_{meta} 3 Hz, ArH), 1.40 (1H, d, J_{meta} 3 Hz, ArH), 1.90 (1H, dd, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-5), 2.41 (1H, dt, J_{ortho} 8 Hz, J_{meta} 2 Hz, H-7), 2.70 (1H, t, J_{ortho} 8 Hz, H-6), 3.30 (1H, d, J_{ortho} 8 Hz, H-8) and 6.67 (3H, s, NMe).

Found: C,50.0%; H,2.9%; N,15.3%; M^+358.

$C_{15}H_{10}N_4O_7$ requires: C,50.3%; H,2.8%; N,15.6%; M 358.

The trituration mother liquors on evaporation gave a red oily solid (0.06g). Leaching with boiling light petroleum gave, after evaporation of the light petroleum extract, 2,4-dinitrophenol (0.04g, 11%), m.p. 108-111° (lit.,[236] 113°), identical (m.p. and i.r. spectrum to an authentic sample.

31. The Preparation of 2-Phenyl-3-(toluene-4-sulphonyloxy)quinazolin-4(3H)-one (353).

The N-hydroxy compound (352) (0.48g, 0.002 mol) in pyridine (2.0 ml)

was treated with stirring at room temperature with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol) and the mixture was stirred at room temperature for 43h. The solution was evaporated and the oily residue was dissolved in chloroform, washed with dilute aqueous sulphuric acid (5.0 ml) and dilute aqueous sodium hydroxide solution (5.0 ml) and evaporated to give 2-phenyl-3-(toluene-4-sulphonyloxy)quinazolin-4(3H)-one (353) (0.70g, 89%; 99% based on unrecovered starting material), as colourless prisms, m.p. 165-166° (decomp.) (from ethanol-dioxan), $\nu_{max.}$ 1715 (CO) cm^{-1}.

Found: C,64.0%; H,4.1%; N,7.0%; M^+392.

$C_{21}H_{16}N_2O_4S$ requires: C,64.3%; H,4.1%; N,7.1%; M 392.

Acidification of the sodium hydroxide washings and extraction with chloroform gave the starting material (352) (0.05g, 10%), identical (m.p. and i.r. spectrum) to an authentic sample.

32. The Hydrolysis of the 3-Sulphonyloxyquinazoline (353).

The 3-sulphonyloxyquinazoline (353) (0.20g, 0.0005 mol) suspended in 10% w/v aqueous sodium hydroxide solution (3.0 ml) was heated under reflux for 15 min. The solution was cooled and acidified to give 3-hydroxy-2-phenylquinazolin-4(3H)-one (352) (0.11g, 92%), m.p. 171-176° (lit.,[222] 177°), identical (m.p. and i.r. spectrum) to an authentic sample.

33. The Attempted Rearrangement of the 3-Sulphonyloxyquinazoline (353).

The 3-sulphonyloxyquinazoline (353) (0.15g, 0.0004 mol) was heated in a cold-finger sublimation apparatus under reduced pressure (water pump) at 170° for 15 min. The solid melted and on cooling was collected (0.14g) and shown (t.l.c. in chloroform over silica and i.r. spectrum) to be a mixture consisting mainly of the starting material (353) and ca. four minor components.

PART 3

1-Hydroxyquinoxaline-2(1H),3(4H)-diones and 3-Phenylquinoxalin-2(1H)-one 4-Oxides

1. The Preparation of the Substituted N-Benzyl-2-nitroanilines (354 c-e).

The N-benzyl-2-nitroanilines were prepared by heating mixtures of the corresponding 2-nitrochlorobenzenes and benzylamine at 150° in the presence of anhydrous potassium carbonate using the method of Kehrmann and Tichwinski [224]

(i) N-Benzyl-2-nitroaniline (354c) (56%) was obtained from 2-nitrochlorobenzene as orange needles, m.p. 66-71° (lit.,[224] 75°).

(ii) N-Benzyl-5-chloro-2-nitroaniline (354d) (82%) was obtained from 2,4-dichloronitrobenzene as orange needles, m.p. 95-100° (lit.,[238] 102°).

(iii) N-Benzyl-5-methyl-2-nitroaniline (354e) (58%) was obtained from 5-methyl-2-nitrochlorobenzene as orange plates, m.p. 94-99° (lit.,[209] 102°).

2. The Preparation of the Substituted 2-Cyano-2'-nitroacetanilides (355 b-e) and (361 a and b).

A solution of cyanoacetic acid (9.0g, 0.105 mol) in dry ether (80 ml) was treated in one portion with phosphorous pentachloride (24g, 0.11 mol). The mixture was stirred for 0.5h and evaporated at room temperature, with the addition of a little dry benzene to azeotrope the last traces of phosphorous oxychloride, to give a red oil which was dissolved in dry benzene (20 ml) and treated with a solution of the corresponding aniline derivative (0.10 mol) in dry benzene (25-100 ml). The mixture was heated under reflux for 2h and

the product was collected from the cooled reaction mixture or isolated after work-up.

(i) N-Methyl-2-nitroaniline (354b) (15.2g) in dry benzene (25 ml) gave on cooling 2-cyano-N-methyl-2'-nitroacetanilide (355b) (20.4g, 93%), m.p. 125-131° (lit.,[225,226] 133°).

(ii) N-Benzyl-2-nitroaniline (354c) (22.8g) in dry benzene (35 ml) gave no product on cooling. Evaporation of the mixture and crystallisation of the residue from ethanol gave N-benzyl-2-cyano-2'-nitroacetanilide (355c) (20.5g, 70%), m.p. 99-102° (lit.,[226] 102°).

(iii) N-Benzyl-5-chloro-2-nitroaniline (354d) (26.3g) in dry benzene (40 ml) gave no product on cooling. Evaporation of the mixture and crystallisation of the residue from ethanol gave N-benzyl-5'-chloro-2-cyano-2'-nitroacetanilide (355d) (25.1g, 77%), as yellow needles, m.p. 143-144°, $\nu_{max.}$ 2250w (CN), 1680 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.05 (1H, d, J_{ortho} 9 Hz, H-3'), 2.44 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-4'), 2.64-3.03 (6H, m, ArH), 5.05 (1H, d, $J_{gem.}$ 14 Hz, benzylic H), 5.39 (1H, d, $J_{gem.}$ 14 Hz, benzylic H) and 6.58 (2H, s, $COCH_2$).

Found: C,58.5%; H,3.8%; N,12.6%; M^+329.

$C_{16}H_{12}ClN_3O_3$ requires: C,58.3%; H,3.7%; N,12.7%; M 329.

(iv) N-Benzyl-5-methyl-2-nitroaniline (354e) (24.2g) in dry benzene (35 ml) gave no solid on cooling. Evaporation of the mixture and crystallisation of the residue from ethanol gave N-benzyl-2-cyano-5'-methyl-2'-nitroacetanilide (355e) (27.5g, 89%), as pale yellow needles, m.p. 124-125°, $\nu_{max.}$ 2250w (CN), 1680 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.15 (1H, d, J_{ortho} 8 Hz, H-3'), 2.57-3.11 (7H, m, ArH), 5.03 (1H, d, $J_{gem.}$ 14 Hz, benzylic H), 5.42 (1H, d, $J_{gem.}$ 14 Hz, benzylic H), 6.68 (1H, s, COCH), 6.71 (1H, s, COCH) and 7.62 (3H, s, Me).

Found: C,66.0%; H,5.0%; N,13.6%; M^+309.

$C_{17}H_{15}N_3O_3$ requires: C,66.0%; H,4.9%; N,13.6%; M 309.

(v) 4-Chloro-2-nitroaniline (360a) (17.2g) in dry benzene (80 ml) gave on cooling 4'-chloro-2-cyano-2'-nitroacetanilide (361a) (22.2g, 92%), as yellow needles, m.p. 189-192° (lit.,[226,228] 192°).

(vi) 4-Methoxy-2-nitroaniline (360b) (16.8g) in dry benzene (100 ml) gave on cooling 2-cyano-4'-methoxy-2'-nitroacetanilide (361b) (22.6g, 96%), as yellow needles, m.p. 132-135° (lit.,[226,228] 134°).

3. The Preparation of the 3-Cyanoquinoxalin-2(1H)-one 4-N-Oxides (362 a and b).

(i) A mixture of the 4-chloro-2-nitroanilide (361a) (4.8g, 0.02 mol) in pyridine (40 ml) and N aqueous sodium hydroxide (20 ml) was stirred at room temperature for 16h, diluted with water (40 ml) and washed with chloroform. The aqueous layer was acidified to give a yellow solid (2.6g) which was extracted with hot ethanol and hot filtered to give 6-chloro-3-cyanoquinoxalin-2(1H)one 4-N-oxide (362a) (2.00g, 45%), m.p. 276-280° (lit.,[226,228] 285°).

(ii) A mixture of the 4-methoxy-2-nitroanilide (361b) (4.7g, 0.02 mol) in pyridine (40 ml) and N aqueous sodium hydroxide (20 ml) was stirred at room temperature for 16h, diluted with water (80 ml) and acidified, with cooling, with concentrated hydrochloric acid. The resulting brown solid was extracted with hot ethanol and hot filtered to give 3-cyano-6-methoxyquinoxalin-2(1H)-one 4-N-oxide (362b) (0.85g, 20%), m.p. 250-256° (lit.,[226,228] 267°). Evaporation of the ethanol mother liquors gave a red solid (2.05g) which was shown by t.l.c. in chloroform-methanol over silica to contain further product (362b), 4-methoxy-2-nitroaniline (360b) and at least five other components.

(iii) The 4-methoxy-2-nitroanilide (361b) (4.7g, 0.02 mol) in absolute ethanol (160 ml) was treated with a solution of sodium (1.8g, 0.08 mol) in absolute ethanol (45 ml) and the mixture was heated under reflux for 0.5h. Evaporation of the mixture, treatment with water

(100 ml) and extraction with chloroform gave 4-methoxy-2-nitroaniline (360b) (1.7g, 51%), m.p. 119-124° (lit.,[237] 129°). Acidification of the aqueous layer gave a yellow solid (1.9g) which on crystallisation from ethanol gave 3-cyano-6-methoxyquinoxalin-2(1H)-one 4-N-oxide (362b) (1.4g, 33%), m.p. 253-258° (lit.,[226,228] 267°).

4. The Methylation of the N-Oxides (362 a and b).

(i) The N-oxide (362a) (1.34g, 0.006 mol) in Analar acetone (280 ml) was treated with anhydrous potassium carbonate (6.9g) and dimethyl sulphate (3.8 ml, 0.038 mol). The mixture was heated under reflux for 4h, hot filtered to remove the inorganic material and evaporated to give a yellow-brown solid which was collected and washed with a little water and ether (1.35g). T.l.c. in ether over Activity III alumina showed it to be a two component mixture. Dry-column chromatography in ether over alumina (93% recovery) gave as the faster-moving component 6-chloro-3-cyano-2-methoxyquinoxaline 4-N-oxide (363a) (0.25g, 18%), as pale yellow prisms, m.p. 186-187° (from ethanol-glacial acetic acid), $\nu_{max.}$ 2200w (CN) and 1150 (C-O) cm^{-1}, τ (CF_3CO_2H) 1.55 (1H, d, J_{meta} 2 Hz, H-5), 1.95-2.20 (2H, m, ArH) and 5.69 (3H, s, OMe).

Found: C,50.8%; H,2.5%; N,17.8%; M^+235.

$C_{10}H_6ClN_3O_2$ requires: C,51.0%; H,2.6%; N,17.8%; M 235.

The slower-moving component was 6-chloro-3-cyano-1-methylquinoxalin-2(1H)-one 4-N-oxide (364a) (0.88g, 64%), deep yellow needles, m.p. 199-200° (from glacial acetic acid), $\nu_{max.}$ 2250w (CN) and 1660 (CO) cm^{-1}, τ (CF_3CO_2H) 1.56 (1H, d, J_{meta} 2 Hz, H-5), 2.05 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-7), 2.31 (1H, d, J_{ortho} 9 Hz, H-8) and 6.10 (3H, s, NMe).

Found: C,51.0%; H,2.5%; N,17.8%; M^+235.

$C_{10}H_6ClN_3O_2$ requires: C,51.0%; H,2.6%; N,17.8%; M 235.

(ii) The N-oxide (362b) (1.95g, 0.009 mol) in Analar acetone (300 ml) was treated with anhydrous potassium carbonate (9.6g) and dimethyl sulphate (5.4 ml, 0.057 mol). The mixture was heated under reflux for 5h and hot filtered to remove inorganic material which was dissolved in water and acidified to give the starting material (362b) (0.20g, 10%), identical (i.r. spectrum) to an authentic sample. Evaporation of the acetone filtrate and trituration of the residue with water and a little ether gave an orange solid (1.60g) whose t.l.c. in ether over Activity III alumina showed it to be a two component mixture. Dry-column chromatography of the orange solid in ethyl acetate over alumina gave as the faster-moving component 3-cyano-2,6-dimethoxyquinoxaline 4-N-oxide (363b) (0.36g, 17%; 20% based on unrecovered starting material), as bright yellow needles, m.p. 212-213° (from ethanol-glacial acetic acid), $\nu_{max.}$ 2200w (CN), τ (CF_3CO_2H) 2.03 (1H, d, J_{ortho} 9 Hz, H-8), 2.10 (1H, d, J_{meta} 2 Hz, H-5), 2.34 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-7), 5.69 (3H, s, OMe) and 5.96 (3H, s, OMe).

Found: C,57.4%; H,4.0%; N,18.3%; M^+231.

$C_{11}H_9N_3O_3$ requires: C,57.1%; H,3.9%; N,18.2%; M 231.

The slower-moving component was 3-cyano-6-methoxy-1-methylquinoxalin-2(1H)-one 4-N-oxide (364b) (1.10g, 53%; 60% based on unrecovered starting material), orange needles, m.p. 262-263° (decomp.) (from dimethylformamide), $\nu_{max.}$ 2200 (CN) and 1640 (CO) cm^{-1}, τ (CF_3CO_2H) 2.11 (1H, m, ArH), 2.31 (2H, m, ArH), 5.99 (3H, s, OMe) and 6.06 (3H, s, NMe).

Found: C,57.2%; H,4.0%; N,18.3%; M^+231.

$C_{11}H_9N_3O_3$ requires: C,57.1%; H,3.9%; N,18.2%; M 231.

5. The Base-catalysed Conversion of the Cyanoquinoxaline N-Oxides (356a) and (364 a and b) into the N-Hydroxyquinoxalines (357a) and (365 a and b)

(i) The N-oxide (365a)[226,228] (2.06g 0.011 mol) in absolute ethanol

(700 ml) was treated with a solution of sodium (1.01g, 0.044 mol) in absolute ethanol (25 ml) and the mixture was heated under reflux on a water bath for 10h. On cooling, the colourless salt was collected (2.0g) and acidified to give a yellow solid (1.48g) which was combined with a second crop (0.32g), obtained by evaporating the ethanol filtrate, treating with water (15 ml) and acidification , to give 1-hydroxyquinoxaline-2(1H),3(4H)-dione (357a) (1.80g, 92%), as a yellow solid, m.p. 275-283° (lit.,[227] 290°).

(ii) The N-oxide (364a) (0.81g, 0.0037 mol) in 20% w/v aqueous potassium hydroxide (3.7 ml) was heated under reflux for 45 min. On cooling, the insoluble salt was collected, washed with chloroform and acidified to give 6-chloro-4-hydroxy-1-methylquinoxaline-2(1H),3(4H)-dione (365a) (0.77g, 92%), as cream needles, m.p. 248-249° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 3200-2400 (OH) and 1695 and 1670 (CO) cm^{-1}, τ (CF_3CO_2H) 2.01-2.10 (1H, m, ArH), 2.42-2.58 (2H, m, ArH) and 6.14 (3H, s, NMe).

Found: C,47.3%; H,3.4%; N,12.4%; M^+226.

$C_9H_7ClN_2O_3$ requires: C,47.7%; H,3.1%; N,12.4%; M 226.

(iii) The N-oxide (364b) (0.92g, 0.004 mol) in 20% w/v aqueous potassium hydroxide (4.0 ml) was heated under reflux for 1h. On cooling, the insoluble salt was collected, washed with chloroform and acidified to give a colourless solid (0.76g) which was combined with a second crop (0.08g) obtained by acidifying the original aqueous mother liquors to give 4-hydroxy-6-methoxy-1-methylquinoxaline-2(1H),3(4H)-dione (365b) (0.84g, 95%), as colourless needles, m.p. 258-259° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 3450 and 3350 (OH), 2650 br (OH) and 1695 and 1660 (CO) cm^{-1}, τ (CF_3CO_2H) 2.39-2.54 (2H, m, ArH), 2.79 (1H, dd, J_{ortho} 9 Hz, J_{meta} 3 Hz, H-7), 5.97 (3H, s, OMe) and 6.13 (3H, s, NMe).

Found: C,53.9%; H,4.7%; N,12.6%; M^+222.

$C_{10}H_{10}N_2O_4$ requires: C,54.1%; H,4.5%; N,12.6%; M 222.

6. The Base-catalysed Conversion of the 2-Cyano-2'-Nitroacetanilides (355 a-c) into the N-Hydroxyquinoxalines (357 a-e).

(i) The anilide (355b) (3.29g, 0.015 mol) in 20% w/v aqueous potassium hydroxide (15 ml) was heated under reflux for 0.5h. On cooling, the insoluble salt was collected, washed with chloroform and acidified to give 4-hydroxy-1-methylquinoxaline-2(1H),3(4H)-dione (357b) (2.23g, 78%), m.p. 240-246° (lit.,[225,226] 254°).

(ii) The anilide (355c) (3.00g, 0.01 mol) in 20% w/v aqueous potassium hydroxide (10 ml) was heated under reflux for 0.5h. On cooling, the insoluble salt was collected, washed with chloroform, combined with the aqueous layer from the filtrate and acidified to give 1-benzyl-4-hydroxyquinoxaline-2(1H),3(4H)-dione (357c) (2.25g, 83%), m.p. 180-184° (lit.,[226] 180°).

(iii) The anilide (355d) (3.30g, 0.01 mol) in 20% w/v aqueous potassium hydroxide (10 ml) was heated under reflux with stirring for 2h. On cooling, the insoluble salt was collected, washed with chloroform and acidified to give 1-benzyl-7-chloro-4-hydroxyquinoxaline-2(1H),3(4H)-dione (357d) (2.50g, 83%), as colourless prisms, m.p. 229-230° (decomp.) (from glacial acetic acid), $\nu_{max.}$ 3200-2500 (OH) and 1690 (CO) cm^{-1}, τ $\left[(CD_3)_2SO\right]$ 2.42 (1H, d, J_{ortho} 9 Hz, H-5), 2.56-2.84 (7H, m, ArH) and 4.58 (2H, s, CH_2).

Found: C,59.4%; H,3.8%; N,9.1%; M^+302.

$C_{15}H_{11}ClN_2O_3$ requires: C,59.5%; H,3.7%; N,9.3%; M 302.

The chloroform washings gave a black gum (0.30g) which was shown by t.l.c. in chloroform-methanol over silica to be a multi-component mixture containing the amine (354d).

(iv) The anilide (355e) (3.10g, 0.01 mol) in 20% w/v aqueous potassium hydroxide (10 ml) was heated under reflux for 0.5h. On cooling, the salt was collected, washed with chloroform and combined with the aqueous layer from the filtrate. Acidification and

extraction with chloroform gave, after trituration with a little ether, 1-benzyl-4-hydroxy-7-methylquinoxaline-2(1H),3(4H)-dione (357e) (1.83g, 65%), as colourless needles, m.p. 232-234° (decomp.) (from glacial acetic acid), $\nu_{max.}$ 3150 br (OH) and 1680 and 1660 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.40-3.01 (8H, m, ArH), 4.60 (2H, s, CH_2) and 7.75 (3H, s, ArMe).

Found: C,68.1%; H,5.1%; N,9.8%; M^+282.

$C_{16}H_{14}N_2O_3$ requires: C,68.1%; H,5.0%; N,9.9%; M 282.

The chloroform washings gave, on trituration with a little ether, a brown solid (1.06g) which was shown by t.l.c. in chloroform-methanol over silica to be an unresolvable three component mixture. Crystallisation from ethanol with hot filtration failed to resolve the mixture.

v) The amide (355a) (2.00g, 0.01 mol) in 20% w/v aqueous potassium hydroxide (20 ml) was heated under reflux for 0.5h. The mixture was cooled, washed with chloroform and acidified to give a brown solid (1.76g) which on crystallisation from aqueous acetic acid gave 1-hydroxyquinoxaline-2(1H),3(4H)-dione (357a) (0.80g, 45%), as pinkish needles, m.p. 280-285° (decomp.) [lit.,[227] 290° (decomp.)]. The mother liquors from the crystallisation gave, on evaporation and trituration with water, a brown solid (0.85g), m.p. 296-302° (decomp.) whose mass spectrum showed the presence of both the N-hydroxyquinoxaline (357a) (M^+178) and quinoxaline-2(1H),3(4H)-dione (370a)[229] (M^+162).

7. The Reduction of the N-Hydroxyquinoxalines (357d) and (365 a and b).

The N-hydroxyquinoxalines (357d) and (365 a and b) (0.002 mol) in glacial acetic acid (10 ml) were heated under reflux for 1.5h with twice their weight of sodium dithionite (added in two portions, the second portion after 0.5h). Hot filtration, evaporation of the filtrate and treatment with water (5.0 ml) gave the product which was washed with carbon disulphide to remove any sulphur present and purified by crystallisation.

(i) The 6-chloro-4-hydroxyquinoxaline (365a) (0.45g) gave 6-chloro-1-methylquinoxaline-2(1H),3(4H)-dione (366a) (0.35g, 85%), as colourless needles, m.p. 332-334° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 3200 (NH) and 1700 and 1670 (CO) cm^{-1}.

Found: C,51.1%; H,3.3%; N,13.5%; M^+210.

$C_9H_7ClN_2O_2$ requires: C,51.3%; H,3.4%; N,13.3%; M 210.

(ii) The 6-methoxy-4-hydroxyquinoxaline (365a) (0.44g) gave 6-methoxy-1-methylquinoxaline-2(1H),3(4H)-dione (366a) (0.36g, 88%), as colourless needles, m.p. 314-316° (decomp.) (from ethanol-dimethylformamide) $\nu_{max.}$ 3150 (NH) and 1695 and 1660 (CO) cm^{-1}.

Found: C,58.6%; H,5.0%; N,13.7%; M^+206.

$C_{10}H_{10}N_2O_3$ requires: C,58.3%; H,4.9%; N,13.6%; M 206.

(iii) The 7-chloro-4-hydroxyquinoxaline (357d) (0.60g) gave 1-benzyl-7-chloroquinoxaline-2(1H),3(4H)-dione (378) (0.56g, 97%), as colourless prisms, m.p. 330-332° (decomp.) (from aqueous dimethylformamide), $\nu_{max.}$ 3150 (NH) and 1705 and 1660 (CO) cm^{-1}.

Found: C,62.3%; H,3.9%; N,9.7%; M^+286.

$C_{15}H_{11}ClN_2O_2$ requires: C,62.8%; H,3.9%; N,9.8%; M 286.

8. The Preparation of the 1,4-Dimethylquinoxaline-2(1H),3(4H)-diones (367 a and b).

The quinoxalines (366 a and b) (0.001 mol) in 10% w/v aqueous sodium hydroxide (2.5 ml) were shaken with dimethyl sulphate (0.5 ml, 0.005 mol) for 18h and the insoluble solid was collected and purified as described.

(i) The 6-chloroquinoxaline (366a) (0.21g) gave a colourless solid (0.21g) which was crystallised from ethanol-dimethylformamide to afford a salt (0.16g), acidification of which yielded starting material (0.14g, 70%), identical (m.p. and i.r. spectrum) to an authentic sample. The crystallisation liquors on evaporation and

treatment with water gave a pale yellow solid (0.03g) which was purified by vacuum sublimation at 180° to give 6-chloro-1,4-dimethylquinoxaline-2(1H), 3(4H)-dione (367a) (0.02g, 10%; 33% based on unrecovered starting material), as colourless prisms, m.p. 192-193° (from ethanol-dimethylformamide), $\nu_{max.}$ 1680 br (CO) cm^{-1}, τ ($CDCl_3$) 2.74-2.82 (3H, m, ArH), 6.38 (3H, s, NMe) and 6.40 (3H, s, NMe).

Found: C,53.5%; H,3.9%; N,12.7%; M^+224.

$C_{10}H_9ClN_2O_2$ requires: C,53.5%; H,4.0%; N,12.5%; M 224.

(ii) The 6-methoxyquinoxaline (366b) (0.20g) gave 6-methoxy-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (367b) (0.10g, 50%; 77% based on unrecovered starting material), as colourless prisms, m.p. 182-183° (from ethanol), $\nu_{max.}$ 1680 br (CO) cm^{-1}, τ ($CDCl_3$) 2.72-2.90 (1H, m, ArH), 3.10-3.30 (2H, m, ArH), 6.15 (3H, s, OMe), 6.42 (3H, s, NMe) and 6.44 (3H, s, NMe).

Found: C,59.9%; H,5.4%; N,12.8%; M^+220.

$C_{11}H_{12}N_2O_3$ requires: C,60.0%; H,5.5%; N,12.7%; M 220.

Acidification of the aqueous filtrate gave starting material (0.07g, 35%), identical (m.p. and i.r. spectrum) to an authentic sample.

9. The Attempted Reaction of the N-Acetoxyquinoxaline (358a) with Acetic Anhydride.

The N-acetoxyquinoxaline (358a)[225] (0.22g, 0.001 mol) in acetic anhydride (2.5 ml) was heated at 100° for 3h. Evaporation of the mixture and trituration of the residue with ether gave starting material (0.22g, quantitative), identical (m.p. and i.r. spectrum) to an authentic sample.

10. The Attempted Reaction of the N-Hydroxyquinoxaline (357b) with Toluene-4-sulphonyl Chloride in the Presence of Sodium Hydroxide.

The N-hydroxyquinoxaline (357b) (0.38g, 0.002 mol) in 10% w/v

aqueous sodium hydroxide (5.0 ml), water (10 ml) and dioxan (10 ml) was treated dropwise with stirring at 45° with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol) in dioxan (1.0 ml), over a period of 2-3 min., and the mixture was stirred for 0.5h. The brown solution was cooled and extracted with chloroform to give a brown intractable gum (0.19g). Acidification of the aqueous mother liquors and extraction with chloroform gave starting material (0.16g, 42%), identical (m.p. and i.r. spectrum) to an authentic sample.

11. The Attempted Reaction of the N-Hydroxyquinoxaline (357b) with Toluene-4-sulphonyl Chloride in the Presence of Triethylamine.

A solution of the N-hydroxyquinoxaline (357b) (0.46g, 0.0024 mol) and triethylamine (0.30g, 0.003 mol) in dimethylformamide (20 ml) at -40° (chlorobenzene-liquid nitrogen bath) was treated with stirring with toluene-4-sulphonyl chloride (0.51g, 0.0027 mol) in dimethylformamide (5.0 ml). After stirring the solution for 5 min., methanol (100 ml) was added and the solution was allowed to reach room temperature and was stirred for 1h. Evaporation and treatment with water (10 ml) gave a pale yellow solid (A) (0.46g), M^+ 210 and 192, which was shown by t.l.c. in chloroform-methanol over silica to be a two component mixture containing no starting material. The mixture was separated by either of two methods as described in (a) and (b) below.

(a) Washing the solid mixture (A) (0.46g) with warm 1M aqueous sodium carbonate gave 7-chloro-1-methylquinoxaline-2(1H),3(4H)-dione (359a) (0.16g, 32%), as colourless prisms, m.p. 302-304° (decomp.) (from ethanol-glacial acetic acid), $\nu_{max.}$ 3200-2600 (NH) and 1690 (CO) cm^{-1}.

Found: C,52.3%; H,3.6%; N,13.7%; M^+210.

$C_9H_7ClN_2O_2$ requires: C,51.3%; H,3.4%; N,13.3%; M 210.

Exact Mass. Found: 210.017904 mass units.

$C_9H_7{}^{35}ClN_2O_2$ requires: 210.019601 mass units.

Found: 212.017448 mass units.

$C_9H_7{}^{37}ClN_2O_2$ requires: 212.016651 mass units.

Acidification of the aqueous filtrate gave a yellow solid (B) (0.21g) which was shown by t.l.c. (as above) to be a two component mixture. The solid mixture (B) was methylated by dissolving it in 10% w/v aqueous sodium hydroxide (2.0 ml) and water (0.5 ml), treating the solution with dimethyl sulphate (0.55 ml, 0.0055 mol) and shaking the mixture for 16h at room temperature. The insoluble colourless solid (0.21g), M^+226 and 220, was collected and was shown by t.l.c. in ethyl acetate over Activity III silica to be a two component mixture with a trace of a third component. Dry-column chromatography in ethyl acetate over silica gave as the slower-moving component 6-methoxy-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (367b) (0.12g, 25%), identical (m.p., mixed m.p. and i.r. spectrum) to a sample prepared as described in 8(ii) above. Also recovered from the column was a pale brown solid (0.14g) which was shown by t.l.c. in chloroform-methanol over silica to be a mixture containing the methoxy compound (367b), the chloro compound (367a) and a trace of a third component.

(b) The solid mixture (A) (0.46g) in 10% w/v aqueous sodium hydroxide (5.5 ml) was treated with dimethyl sulphate (1.1 ml, 0.011 mol) and the mixture was shaken at room temperature for 17h to give a colourless solid (0.21g) which was combined with a second crop (0.20g) obtained by extraction of the filtrate with chloroform. T.l.c. of the combined solid in ethyl acetate over Activity III alumina showed it to be a two component mixture with a trace of a third component. Dry-column

chromatography in ethyl acetate over alumina gave as the faster-moving component 6-chloro-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (367a) (0.03g, 7%), identical (m.p., mixed m.p. and i.r. spectrum) to a sample prepared as described in 8(i), above, and as the slower-moving component 6-methoxy-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (367b) (0.26g, 50%), identical (m.p., mixed m.p. and i.r. spectrum) to a sample prepared as described in 8(ii), above. An intermediate fraction gave a pale brown solid (0.12g) which was shown by t.l.c. in chloroform-methanol over silica to be a mixture containing mainly the chloro compound (367a), with a small quantity of the methoxy compound (367b) and a trace of a third component.

12. The Attempted Reaction of the N-Hydroxyquinoxaline (357b) with Toluene-4-sulphonyl Chloride in Dimethylformamide.

The N-hydroxyquinoxaline (357b) (0.40g, 0.002 mol) and toluene-4-sulphonyl chloride (0.42g, 0.0022 mol) in dimethylformamide (5.0 ml) were heated at 100° for 1h. Evaporation of the mixture and treatment with water (5.0 ml) gave a pale solid (0.28g), M^+ 210 and 192, which was shown by t.l.c. in chloroform-methanol over silica to be a two component mixture of the quinoxalines (359a) and (359b), identical (mass and i.r. spectra and t.l.c.) to the mixture (A) obtained as described in 11., above. Extraction of the aqueous filtrate with chloroform gave a pale brown solid (0.15g) which was shown by t.l.c. (as above) to be an unresolvable multi-component mixture.

13. The Attempted Reaction of the N-Hydroxyquinoxaline (357b) with Toluene-4-sulphonyl Chloride in the Presence of Sodium Acetate and Triethylamine.

A solution of the N-hydroxyquinoxaline (357b) (0.46g, 0.0024 mol),

triethylamine (0.41g, 0.003 mol) and sodium acetate (0.45g, 0.0055 mol) in dimethylformamide (50 ml) and water (15 ml) was treated with stirring at -40° with toluene-4-sulphonyl chloride (0.51g, 0.0027 mol) in dimethylformamide (2.0 ml). The mixture was stirred for 0.5h at -40° and then allowed to reach room temperature. Evaporation of the green solution and treatment with water (10 ml) gave a yellow solid (0.36g), M^+210 and 192, which was shown by t.l.c. in chloroform-methanol over silica to be a two component mixture of the quinoxalines (359a) and (359b), identical (mass and i.r. spectra and t.l.c.) to the mixture (A) obtained as described in 11., above.Extraction of the filtrate with chloroform gave a pale brown solid (0.10g) which was shown by t.l.c. (as above) to be a five component mixture.

14. The Reactions of the N-Hydroxyquinoxalines (357 a-e) with Toluene-4-sulphonyl Chloride in Pyridine.

The N-hydroxyquinoxalines (357 a-e) (0.002 mol) suspended in pyridine (5-10 ml) were treated with stirring at room temperature with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol). The starting material dissolved and heat was evolved. Stirring was continued at room temperature for 1h. Any insoluble material was collected from the mixture which was worked up as described for individual reactions below.

(i) The mixture from 1-hydroxyquinoxaline-2(1H),3(4H)-dione (357a) (0.36g) in pyridine (5.0 ml) was evaporated and triturated with a little chloroform to give a brown solid (0.37g) which was crystallised from aqueous dimethylformamide to give a pale solid (0.27g), m.p. > 360°, $\nu_{max.}$ 3250-2500 (NH) and 1690 br (CO) cm^{-1}, M^+162 (minor peak at m/e 196). A further crystallisation gave the pure quinoxaline-2(1H),3(4H)-dione (370a) (0.20g, 62%), m.p. > 360°, M^+162, identical (m.p. and mass and i.r. spectra) to an authentic sample. No further material was obtained from the original chloroform washings.

(ii) The mixture from the 4-hydroxy-1-methylquinoxaline (357b) (0.39g) in pyridine (10 ml) gave an insoluble salt (0.68g) which on dissolving in water and basifying with dilute aqueous sodium hydroxide gave anhydro 1-(1,4-dihydro-1-methyl-2,3-dioxoquinoxalin-7-yl)pyridinium hydroxide (371a) (0.51g, quantitative), as yellow needles (from water) which decompose without melting < 270°, $\nu_{max.}$ 3500 and 3400-3100 (OH) and 1605 (CO) cm^{-1}, τ (CF_3CO_2H) 0.95 (2H, m, ArH), 1.19 (1H, m, ArH), 1.68 (2H, m, ArH), 2.11 (1H, s, ArH), 2.27 (2H, s, ArH) and 6.12 (3H, s, NMe).

Found: C,54.9%; H,4.7%; N,13.6%; M^+254.

$C_{14}H_{11}N_3O_2$ requires: C,66.4%; H,4.4%; N,16.6%; M 253.

$C_{14}H_{15}N_3O_5$ requires: C,55.1%; H,5.0%; N,13.8%.

Treatment of a suspension of the betaine (371a), in acetone, with concentrated hydrochloric acid gave 1-(1,4-dihydro-1-methyl-2,3-dioxoquinoxalin-7-yl)pyridinium chloride (372), as colourless prisms, m.p. > 350° (from aqueous ethanol), $\nu_{max.}$ 3350 (NH) and 1695 and 1685 (CO) cm^{-1}.

Found: C,52.4%; H,4.5%; N,13.4%; M^+254.

$C_{14}H_{12}ClN_3O_2$ requires: C,58.0%; H,4.2%; N,14.5%; M 254 (cation).

$C_{14}H_{14}ClN_3O_4$ requires: C,51.9%; H,4.4%; N,13.0%.

Exact mass. Found: 254.094923 mass units.

$C_{14}H_{12}N_3O_2$ requires: 254.092946 mass units.

(iii) The mixture from the 1-benzyl-4-hydroxyquinoxaline (357c) (0.54g) in pyridine (5.0 ml) gave an insoluble salt (0.80g) which was dissolved in water and basified with dilute aqueous sodium hydroxide to give anhydro 1-(1-benzyl-1,4-dihydro-2,3-dioxoquinoxalin-7-yl)-pyridinium hydroxide (371b) (0.62g, 95%), as orange prisms (from aqueous ethanol), which decompose without melting < 205°, $\nu_{max.}$ 3600-2800 (OH) and 1645 and 1610 (CO) cm^{-1}.

Found: C,66.0%; H,5.0%; N,11.8%; M^+267.

$C_{20}H_{15}N_3O_2$ requires: C,72.9%; H,4.6%; N,12.8%; M 329.

$C_{20}H_{17}N_3O_4$ requires: C,65.9%; H,5.0%; N,11.5%.

(iv) The mixture from the 1-benzyl-7-chloroquinoxaline (357d) (0.60g) in pyridine (5.0 ml) was evaporated under reduced pressure and the residue was treated with dilute aqueous sulphuric acid (10 ml) and extracted with chloroform to give a brown solid (0.39g) which was shown by t.l.c. in chloroform-methanol over silica to be a mixture of at least three components. Two recrystallisations from ethanol with charcoal clarification failed to resolve the mixture which was not further investigated. Basification of the aqueous layer with saturated aqueous sodium bicarbonate and extraction with chloroform gave a brown oil (0.11g) which was shown by t.l.c. (as above) to be at least four components.

(v) The mixture from the 1-benzyl-7-methylquinoxaline (357e) (0.56g) in pyridine (5.0 ml) was evaporated and the residue was treated with dilute aqueous sulphuric acid (5.0 ml) and extracted with chloroform to give a brown solid (0.49g) which was shown by t.l.c. in chloroform-methanol over silica to be an unresolvable multi-component mixture. Basification of the aqueous layer with sodium acetate and extraction with chloroform gave a pale yellow solid (0.09g) which was shown by t.l.c. (as above) to be a four component mixture. Crystallisation from ethanol-light petroleum gave 1-(1-benzyl-1,4-dihydro-2,3-dioxoquinoxalin-7-ylmethyl)pyridinium toluene-4-sulphonate (381) (0.04g, 4%), as a colourless amorphous solid, m.p. 189-190°, $\nu_{max.}$ 3200-2500 (NH) and 1700 (CO) cm^{-1}.

Found: C,64.4%; H,4.9%; N,8.0%; M^+344.

$C_{28}H_{25}N_3O_5S$ requires: C,65.2%; H,4.9%; N,8.2%; M 344 (cation).

15. The Methylation of the Betaine (371a).

The betaine (371a) (1.00g, 0.004 mol) suspended in redistilled dimethylformamide (25 ml) was treated with methyl iodide (6.0 ml, 0.096 mol) and the mixture was stirred at 75° for 1h. The cooled solution was poured into dry ether (200 ml) and cooled in ice to give 1-(1,4-dihydro-1,4-dimethyl-2,3-dioxoquinoxalin-7-yl)pyridinium iodide (373) (1.40g, 90%), as yellow prisms, m.p. 319-320° (decomp.) (from aqueous ethanol), $\nu_{max.}$ 1675 (CO) cm^{-1}, τ (D_2O) 0.79 (2H, m, ArH), 1.19 (1H, m, ArH), 1.67 (2H, m, ArH), 2.05-2.13 (3H, m, ArH) and 6.32 (6H, s, NMe).

Found: C,45.3%; H,3.4%; N,10.8%; M^+268.

$C_{15}H_{14}IN_3O_2$ requires: C,45.6%; H,3.6%; N,10.6%; M 268 (cation).

16. The Reaction of the N-Oxides (382 a-d) and (379a) with Toluene-4-sulphonyl Chloride in Pyridine.

The N-oxide (0.002 mol) in pyridine was treated with stirring at 60° with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol) and the mixture was stirred at 60° for 5-22h and worked up as described for the individual reactions below.

(i) The mixture from 1-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382a)[231] (0.50g) in pyridine (4.0 ml) gave 1-(1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalin-7-yl)pyridinium toluene-4-sulphonate (384a) (0.65g. 67%; 86% based on unrecovered starting material), as pale yellow needles, m.p. 220-221° (from ethanol), $\nu_{max.}$ 1660 (CO) cm^{-1}, τ (CF_3CO_2H) 0.83 (2H, m, ArH), 1.06-1.43 (2H, m, ArH), 1.55-1.85 (5H, m, ArH), 1.93-2.46 (6H, m, ArH), 2.75 (2H, d, J_{ortho} 8 Hz, ArH), 5.95 (3H, s, NMe) and 7.63 (3H, s, ArMe).

Found: C,66.5%; H,4.9%; N,8.8%; M^+314.

$C_{27}H_{23}N_3O_4S$ requires: C,66.8%; H,4.8%; N,8.7%; M 314 (cation).

Evaporation of the pyridine filtrate and trituration with water gave, after washing with ether, starting material (382a) (0.11g, 22%), identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) The mixture from 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382b)[231] (0.57g) in pyridine (10 ml) after 22h gave a pale yellow salt (0.30g), m.p. 244-288° (decomp.) which on treatment with concentrated hydrochloric acid, followed by water, gave 1-(6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalin-7-yl)-pyridinium chloride (384b) (0.22g, 29%), as pale yellow needles, m.p. 305-308° (decomp.) (from aqueous ethanol), $\nu_{max.}$ 1660 (CO) cm^{-1}, τ (CF_3CO_2H) 0.88-1.19 (3H, m, ArH), 1.33 (1H, s, H-8), 1.50-1.86 (5H, m, ArH), 2.08-2.41 (3H, m, ArH) and 6.00 (3H, s, NMe).

Found: C,57.2%; H,4.2%; N,10.1%; M^+348.

$C_{20}H_{15}Cl_2N_3O$ requires: C,62.5%; H,3.9%; N,10.9%; M 348 (cation).

$C_{20}H_{17}Cl_2N_3O_3$ requires: C,57.4%; H,4.1%; N,10.1%.

Exact Mass. Found: 348.089619 mass units.

$C_{20}H_{15}{}^{35}ClN_3O$ requires: 348.090358 mass units.

Found: 350.089133 mass units.

$C_{20}H_{15}{}^{37}ClN_3O$ requires: 350.087408 mass units.

Evaporation of the pyridine filtrate and treatment with dilute aqueous sulphuric acid (5.0 ml) gave a pale yellow solid (0.50g) which was crystallised twice from ethanol-dimethylformamide to give starting material (382b) (0.24g, 42%), identical (m.p. and i.r. spectrum) with an authentic sample. The crystallisation mother liquors on evaporation gave a yellow solid (0.18g) which was shown by t.l.c. in chloroform-methanol over silica to be a mixture of at least four components, one of which was starting material (382b). Dry-column chromatography in ether over alumina gave starting material (382b) (0.02g, 4%), a brown solid (0.06g), which was shown by t.l.c. to be a multi-component mixture containing starting material

(382b), and a yellow solid (0.09g), t.l.c. of which showed the presence of two components, τ ($CDCl_3$) 1.66-1.82 (3 units, m, ArH), 2.03 (1 unit, s, ArH), 2.12-2.28 (2 units, m, ArH), 2.46-2.84 (10 units, m, ArH), and 6.25-6.36 (4 units, m, NMe), M^+304, one of which was identified as 6,7-dichloro-1-methyl-3-phenylquinoxalin-2(1H)-one (391a) by comparison (^1H n.m.r. and mass spectra) with an authentic sample[231].

(iii) The mixture from 1,6-dimethyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382c)[231] (0.53g) in pyridine (10 ml) after 22h gave 1-(1,2-dihydro-1,6-dimethyl-2-oxo-3-phenylquinoxalin-7-yl)pyridinium toluene-4-sulphonate (384c) (0.17g, 17%), as pale yellow needles, m.p. 225-227° (decomp.) (from ethanol), $\nu_{max.}$ 1645 (CO) cm^{-1}, τ (CF_3CO_2H) 0.91-1.19 (3H, m, ArH), 1.49-1.88 (6H, m, ArH), 2.05-2.42 (5H, m, ArH), 2.72 (2H, d, J_{ortho} 8 Hz, ArH), 5.98 (3H, s, NMe), 7.60 (3H, s, ArMe) and 7.64 (3H, s, ArMe).

Found: C,65.3%; H,5.0%; N,8.2%; M^+328.

$C_{28}H_{25}N_3O_4S$ requires: C,67.3%; H,5.1%; N,8.4%; M 328 (cation).

$C_{28}H_{25}N_3O_5S$ requires: C,65.2%; H,4.9%; N,8.2%.

Exact Mass Found: 328.144260 mass units.

$C_{21}H_{18}N_3O$ requires: 328.144979 mass units.

Evaporation of the pyridine solution and treatment with dilute aqueous sulphuric acid (5.0 ml) gave a pale yellow solid (0.45g) which on crystallisation from aqueous dimethylformamide afforded starting material (382c) (0.24g, 46%), identical (m.p. and i.r. spectrum) to an authentic sample. The crystallisation mother liquors on evaporation gave a pale yellow solid (0.15g) which was shown by t.l.c. in chloroform-methanol over silica to be a two component mixture containing a trace of starting material. Treatment of the solid with dilute aqueous sodium hydroxide caused a deep red colour and gave an insoluble, intractable solid (0.09g). Acidification

of the filtrate gave an unidentified pale brown solid (0.02g), m.p. 287-293° (decomp.), $\nu_{max.}$ 3400 (OH) and 1645 (CO) cm^{-1}, M^+338.

(iv) The mixture from 6-methoxy-1-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382d)[231] (0.56g) in pyridine (20 ml) after 4h gave, on evaporation and trituration of the residue with water, starting material (382d) (0.54g, 97%), identical (m.p. and i.r. spectrum) to an authentic sample.

The N-oxide (382d)[231] (0.56g) in pyridine (20 ml) was heated under reflux with toluene-4-sulphonyl chloride (0.42g) and the mixture was cooled, evaporated and triturated with water to give starting material (382d) (0.54g, 97%), identical (m.p. and i.r. spectrum) with an authentic sample.

(v) 1,6,7-Trimethyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (379a)[230,231] (0.56g) in pyridine (10 ml) was stirred at room temperature with toluene-4-sulphonyl chloride (0.42g). T.l.c. of the mixture in chloroform-methanol over silica after 66 and 90h showed the presence of starting material and two other components. More toluene-4-sulphonyl chloride (0.42g) was added and stirring was continued at room temperature for a further 26h. Evaporation of the mixture and trituration with water (10 ml) gave a yellow solid (0.42g) which was shown by t.l.c. in chloroform-methanol over silica to be a two component mixture. Dry-column chromatography in ether over alumina gave as the faster-moving component 8-chloro-1,6,7-trimethyl-3-phenylquinoxalin-2(1H)-one (393) (0.09g, 15%), as pale yellow needles, m.p. 155-157° (lit.,[209] 157°), $\nu_{max.}$ 1650 (CO) cm^{-1}, τ ($CDCl_3$), 1.66-1.81 (2H, m, ArH), 2.44 (1H, s, H-5), 2.50-2.65 (3H, m, ArH), 6.04 (3H, s, NMe), 7.58 (3H, s, ArMe) and 7.64 (3H, s, ArMe), identical (m.p., mixed m.p. and i.r. and ^1H n.m.r. spectra) to an authentic sample, and as the slower-moving component, 5-chloro-1,6,7-trimethyl-3-phenylquinoxalin-2(1H)-one (394) (0.18g, 30%), pale yellow needles, m.p. 194-195° (lit.,[209] 196°), $\nu_{max.}$ 1660 and 1640 (CO) cm^{-1}, τ ($CDCl_3$) 1.46-1.61 (2H,

m, ArH), 1.51-1.69 (3H, m, ArH), 3.24 (1H, s, H-8), 6.48 (3H, s, NMe), 7.71 (3H, s, ArMe) and 7.75 (3H, s, ArMe), identical (m.p., mixed m.p. and i.r. and ^{1}H n.m.r. spectra) to an authentic sample. An intermediate fraction yielded a yellow solid (0.12g), m.p. 139-170°, which was shown by t.l.c. in chloroform-methanol over silica and by its ^{1}H n.m.r. spectrum to be a 1:1 mixture of the two isomers (393) and (394).

The original aqueous mother liquors were extracted with chloroform and the extract was dried over anhydrous magnesium sulphate. At this stage, a colourless solid separated from the chloroform extract. The drying agent was collected and dissolved in water to give, as an insoluble solid, 1-(1,2-dihydro-1,6-dimethyl-2-oxo-3-phenylquinoxalin-7-ylmethyl)pyridinium toluene-4-sulphonate (395a) (0.03g, 3%), pale yellow prisms, m.p. 249-250° (from ethanol), $\nu_{max.}$ 1650 (CO) cm^{-1}, τ (CF_3CO_2H) 1.02-1.15 (2H, m, ArH), 1.25-1.48 (2H, m, ArH), 1.67-1.94 (5H, m, ArH), 1.97 (1H, s, H-5), 2.05-2.40 (4H, m, ArH), 2.72 (2H, d, J_{ortho} 8 Hz, ArH), 3.77 (2H, s, CH_2), 5.96 (3H, s, NMe), 7.53 (3H, s, ArMe) and 7.60 (3H, s, ArMe).

Found: C,67.6%; H,5.3%; N,8.1%.

$C_{29}H_{27}N_3O_4S$ requires: C,67.8%; H,5.3%; N,8.2%.

The chloroform extract, on evaporation, yielded no material.

17. The Reaction of the N-Oxides (382 e-h) and (379b) with Toluene-4-sulphonyl Chloride in Pyridine.

The corresponding N-oxide (0.002 mol) in pyridine was treated with stirring at 60° with toluene-4-sulphonyl chloride (0.42g, 0.0022 mol) and the mixture was stirred at 60° for 3h. The mixture (containing an insoluble salt) was worked up as described for the individual reactions below.

(i) The mixture from 3-phenylquinoxalin-2(1H)-one 4-N-oxide (382e)[231] (0.48g) in pyridine (8.0 ml) gave a colourless salt (0.32g), m.p. 282-303°

(decomp.) which was suspended in water and basified with solid sodium bicarbonate to give anhydro 1-(1,2-dihydro-2-oxo-3-phenylquinoxalin-7-yl)-pyridinium hydroxide (392a) (0.26g, 44%), as orange needles (from aqueous ethanol) which decompose without melting at 225-235°, $\nu_{max.}$ 3400 br and 1630w (CO) cm^{-1}.

Found: C,72.1%; H,4.2%; N,13.2%; M^+300.

$C_{19}H_{13}N_3O$ requires: C,76.2%; H,4.4%; N,14.0%; M 299.

$C_{19}H_{13}N_3O_2$ requires: C,72.4%; H,4.2%; N,13.3%.

Evaporation of the pyridine solution, treatment with dilute aqueous sulphuric acid (5.0 ml) and crystallisation of the resultant oily solid from ethanol-dimethylformamide gave a pale yellow solid (0.25g), m.p. 230-256°, $\nu_{max.}$ 1660, 1625 and 1610 (CO) cm^{-1}, M^+ 256 and 238, which was shown by t.l.c. in chloroform-methanol over silica to be an unresolvable three component mixture containing starting material (382e) and 7-chloro-3-phenylquinoxalin-2(1H)-one (391c)[231]. Crystallisation from ethanolic or aqueous dimethylformamide failed to resolve the mixture.

(ii) The mixture from 6-chloro-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382f)[231] (0.55g) in pyridine (10 ml) gave a colourless salt (0.20g) which was dissolved in water and basified with solid sodium bicarbonate to give anhydro 1-(6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalin-7-yl)pyridinium hydroxide (392b) (0.15g, 24%), as yellow needles(from aqueous ethanol) which decompose without melting at 234-244°, $\nu_{max.}$ 1660w (CO) and 1630w cm^{-1}, τ (CF_3CO_2H) 0.96-1.19 (3H, m, ArH), 1.52 (1H, s, H-8), 1.53-1.86 (4H, m, ArH), 1.87 (1H, s, H-5) and 2.17-2.48 (3H, m, ArH).

Found: C,64.5%; H,4.0%; N,11.8%; M^+271.

$C_{19}H_{12}ClN_3O$ requires: C,68.4%; H,3.6%; N,12.6%; M 333.

$C_{19}H_{14}ClN_3O_2$ requires: C,64.9%; H,4.0%; N,11.9%.

Evaporation of the pyridine solution, treatment with dilute aqueous sulphuric acid (5.0 ml) and crystallisation of the resultant oily solid from ethanol-dimethylformamide gave a pale yellow solid (0.39g), m.p. 255-290°, $\nu_{max.}$ 1660 and 1625 (CO) cm^{-1}, τ (CF_3CO_2H) 1.48 (2 units, d, J_{meta} 2 Hz, ArH), 1.72 (1 unit, s, ArH), 1.74-1.86 (2 units, m, ArH) and 2.08-2.48 (20 units, m, ArH), M^+290 and 272, which was shown by t.l.c. in chloroform-methanol over silica to be an unresolvable mixture of four components containing mainly starting material (382f) and also 6,7-dichloro-3-phenylquinoxalin-2(1H)-one (391d)[231]. Crystallisation from aqueous dimethylformamide failed to resolve the mixture.

(iii) The mixture from 6-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382g)[231] (0.50g) in pyridine (8.0 ml) gave a pale yellow salt (0.45g), m.p. 265-300° (decomp.), which was dissolved in water and basified with solid sodium bicarbonate to give anhydro 1-(1,2-dihydro-6-methyl-2-oxo-3-phenylquinoxalin-7-yl)pyridinium hydroxide (392c) (0.32g, 52%), as brilliant yellow needles (from ethanol) which decompose without melting at 258-260°, $\nu_{max.}$ 3400 (OH) and 1625w (CO) cm^{-1}, τ (CF_3CO_2H) 0.98-1.14 (3H, m, ArH), 1.52-1.83 (5H, m, ArH), 1.97 (1H, s, H-5), 2.06-2.42 (3H, m, ArH) and 7.66 (3H, s, ArMe).

Found: C,72.5%; H,5.3%; N,12.7%; M^+314.

$C_{20}H_{15}N_3O$ requires: C,76.7%; H,4.8%; N,13.4%; M 313.

$C_{20}H_{17}N_3O_2$ requires: C,72.5%; H,5.2%; N,12.7%.

Evaporation of the pyridine filtrate, treatment with dilute aqueous sulphuric acid (5.0 ml) and crystallisation of the gummy solid from ethanol-dimethylformamide gave 7-chloro-6-methyl-3-phenylquinoxalin-2(1H)-one (391e) (0.15g, 28%), as pale yellow prisms, m.p. 267-268° (lit.,[231] 270°), identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample.

(iv) The mixture from 6-methoxy-3-phenylquinoxalin-2(1H)-one 4-N-oxide (382h)[231] (0.54g) in pyridine (20 ml) gave a colourless salt (0.06g) which on treatment with water and basification with solid sodium bicarbonate gave anhydro 1-(1,2-dihydro-6-methoxy-2-oxo-3-phenylquinoxalin-7-yl)pyridinium hydroxide (392d) (0.05g, 7%), as orange needles (from aqueous ethanol) which decompose without melting at 210-212°, $\nu_{max.}$ 3500-3100 (OH) and 1630w (CO) cm^{-1}, τ (CF_3CO_2H) 0.94-1.24 (3H, m, ArH), 1.45-1.97 (6H, m, ArH), 2.05-2.38 (3H, m, ArH) and 5.91 (3H, s, OMe).

Found: C,60.3%; H,4.8%; N,10.6%.

$C_{20}H_{15}N_3O_2$ requires: C,72.9%; H,4.6%; N,12.8%.

$C_{20}H_{19}N_3O_6$ requires: C,60.5%; H,4.5%; N,10.6%.

Evaporation of the pyridine filtrate and trituration of the residue with water gave starting material (382h) (0.50g, 93%), m.p. 270-279° (lit.,[239] 297-300°), identical (m.p. and i.r. spectrum) to an authentic sample.

Heating the N-oxide (382h) (0.54g) and toluene-4-sulphonyl chloride (0.42g) in pyridine (20 ml) under reflux for 2h gave no salt. Work up gave a yellow solid (0.52g) which was shown by t.l.c. in chloroform-methanol over silica to be mainly starting material (382h) with traces of at least seven other components.

(v) 6,7-Dimethyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (379b)[230,231] (0.53g) in pyridine (25 ml) was stirred at room temperature with toluene-4-sulphonyl chloride (0.42g). T.l.c. of the mixture in chloroform-methanol over silica after 66 and 90h showed the presence of starting material and two other components. After 90h, more toluene-4-sulphonyl chloride (0.42g) was added and stirring was continued for a further 26h to give 1-(1,2-dihydro-6-methyl-2-oxo-3-phenylquinoxalin-7-ylmethyl)pyridinium chloride (295b) (0.35g, 49%), as pale yellow needles, m.p. 236-237° (aqueous

ethanol), $\nu_{max.}$ 1645 (CO) cm^{-1}, τ (CF_3CO_2H) 1.02-1.17 (2H, m, ArH), 1.22-1.41 (1H, m, ArH), 1.62-1.90 (5H, m, ArH), 1.99-2.40 (4H, m, ArH), 3.84 (2H, s, CH_2) and 7.48 (3H, s, ArMe).

Found: C,66.2%; H,4.9%; N,11.0%.

$C_{21}H_{18}ClN_3O$ requires: C,69.3%; H,5.0%; N,11.6%.

$C_{21}H_{20}ClN_3O_2$ requires: C,66.0%; H,5.3%; N,11.0%.

Evaporation of the pyridine filtrate and treatment with dilute aqueous sulphuric acid (5.0 ml) gave a yellow solid (0.25g) which was shown by t.l.c. in chloroform-methanol over silica to be a multi-component mixture containing no starting material. Crystallisation from ethanol, with hot filtration, or ethanol-dimethylformamide failed to resolve the mixture.

18. The Reaction of the 1-Hydroxyquinoxaline 4-N-Oxides (383 a and b) With Toluene-4-sulphonyl Chloride in Pyridine.

The N-hydroxyquinoxaline (383 a or b)[231] (0.002 mol) in pyridine (4.0 ml) was treated with stirring with toluene-4-sulphonyl chloride (0.84g, 0.0044 mol) and the mixture was stirred at room temperature or at 60° for 1-4h and any insoluble solid was collected. Evaporation of the filtrate, treatment with dilute aqueous sulphuric acid (5.0 ml) and extraction with chloroform gave further product .

(i) 1-Hydroxy-3-phenylquinoxalin-2(1H)-one 4-N-oxide (383a)[231] (0.51g) heated at 60° for 4h gave a colourless insoluble salt (0.13g), m.p. 304-319° (decomp.) which was dissolved in water and basified with solid sodium bicarbonate to give anhydro 1-(1,2-dihydro-1-hydroxy-2-oxo-3-phenylquinoxalin-7-yl)pyridinium hydroxide (404) (0.08g, 13%), as orange needles (from aqueous ethanol) which decompose without melting at 244-247°.

Found: C,68.5%; H,4.5%; N,12.6%; M^+316.

$C_{19}H_{13}N_3O_2$ requires: C,72.4%; H,4.2%; N,13.3%; M 315.

$C_{19}H_{15}N_3O_3$ requires: C,68.5%; H,4.5%; N,12.6%.

Further work up as described before gave a brown gum (0.47g) which was shown by t.l.c. in chloroform-methanol over silica to be at least five components. Trituration with methanol gave an unidentified pale brown solid (0.03g), m.p. 257-259° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 1650 (CO) cm^{-1}.

Found: C,63.8%; H,3.4%; N,10.6%; M^+290.

Work up of the methanol mother liquors gave no further material.

(ii) The reaction of 7-chloro-1-hydroxy-3-phenylquinoxalin-2(1H)-one 4-N-oxide (383b)[231] (0.58g) with toluene-4-sulphonyl chloride in pyridine at room temperature for 1h gave 7-chloro-3-phenyl-1-(toluene-4-sulphonyloxy)quinoxalin-2(1H)-one 4-N-oxide (405) (0.87g, 99%), as colourless prisms, m.p. 155-156° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 1680 (CO) cm^{-1}, τ ($CDCl_3$) 1.67 (1H, d, J_{ortho} 9 Hz, H-5), 1.98 (2H, d, J_{ortho} 8 Hz, ArH), 2.24-2.40 (3H, m, ArH), 2.48-2.72 (6H, m, ArH) and 7.54 (3H, s, ArMe).

Found: C,56.9%; H,3.4%; N,6.3%; M^+442.

$C_{21}H_{15}ClN_2O_5S$ requires: C,57.0%; H,3.4%; N,6.3%; M 442.

(iii) The reaction of 7-chloro-1-hydroxy-3-phenylquinoxalin-2(1H)-one 4-N-oxide (383b)[231] (0.58g) with toluene-4-sulphonyl chloride in pyridine at 60° for 2h gave a dark red gum (0.72g) which on trituration with ether-methanol gave the 1-(toluene-4-sulphonyloxy)quinoxaline (405) (0.37g, 42%), identical (m.p. and i.r. spectrum) to an authentic sample. T.l.c. in chloroform-methanol over silica showed that the filtrate contained an unresolvable multi-component mixture.

19. The Hydrolysis of the 1-(Toluene-4-sulphonyloxy)quinoxaline (405).

The 1-(toluene-4-sulphonyloxy)quinoxaline (405) (0.22g, 0.0005 mol)

was suspended in 10% w/v aqueous sodium hydroxide (2.5 ml) and stirred at 50° for 1.5h. The insoluble starting material (405) was collected (0.12g, 55%), identical (m.p. and i.r. spectrum) to an authentic sample. Acidification of the alkaline filtrate gave 7-chloro-1-hydroxy-3-phenylquinoxalin-2(1H)-one 4-N-oxide (383b) (0.06g; 42%; 90% based on unrecovered starting material), identical (m.p. and i.r. spectrum) to an authentic sample.

20. The Attempted Reaction of the 1-(Toluene-4-sulphonyloxy)-quinoxaline (405) with Glacial Acetic Acid.

(i) The 1-(toluene-4-sulphonyloxy)quinoxaline (405) (0.22g, 0.0005 mol) was heated under reflux with glacial acetic acid (3.0 ml) for 45 min. The mixture was evaporated to give a very dark intractable oil (0.20g) which was shown by t.l.c. in chloroform-methanol over silica to be a multi-component mixture.

(ii) The 1-(toluene-4-sulphonyloxy)quinoxaline (405) (0.22g, 0.0005 mol) in glacial acetic acid (25 ml) was treated with fused sodium acetate (0.17g, 0.002 mol) and the solution was stirred at room temperature for 17h. Evaporation of the mixture at room temperature and treatment with water (5.0 ml) gave starting material (405) (0.21g, 95%), identical (m.p. and i.r. spectrum) to an authentic sample.

21. The Attempted Hydrolytic Cleavage of the Betaine (371a) using Sodium Hydroxide.

The betaine (371a) (0.50g, 0.002 mol) suspended in 10% w/v aqueous sodium hydroxide (5.0 ml) was stirred at 75° for 1h. The insoluble starting material was collected (0.37g, 74%) and identified (i.r. spectrum) by comparison with an authentic sample. The aqueous filtrate after washing with chloroform was acidified to give a dark

intractable solid (0.02g). Neutralisation of the aqueous filtrate with sodium acetate and extraction with chloroform gave a negligible quantity of red oil.

22. The Reaction of the Pyridinium Salts (373) and (384a) with Piperidine.

The pyridinium salt (373) or (384a) (0.002 mol) in piperidine (4.0 ml), methanol (4.0 ml) and water (2.0 ml) was heated under reflux for 1h. The mixture was cooled in ice and scratched to give the product.

(i) The pyridinium iodide (373) (0.80g) gave 6-amino-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (374b) (0.32g, 78%), as yellow prisms, m.p. 313-315° (decomp.) (from aqueous dimethylformamide), $\nu_{max.}$ 3450, 3350 and 3200 (NH_2) and 1680 and 1660 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.93 (1H, d, J_{ortho} 8 Hz, H-8), 3.39-3.59 (2H, m, ArH), 4.81 (2H, s, NH_2) and 6.63 (6H, s, NMe).

Found: C,58.5%; H,5.7%; N,20.4%; M^+205.

$C_{10}H_{11}N_3O_2$ requires: C,58.5%; H,5.4%; N,20.5%; M 205.

Evaporation of the filtrate, treatment with dilute aqueous sulphuric acid (10 ml) and extraction with chloroform gave a purple intractable gum (0.80g). Basification of the aqueous layer with solid sodium bicarbonate and extraction with chloroform gave an intractable red gum (0.02g).

(ii) The pyridinium toluene-4-sulphonate (384a) (1.0g) gave no solid. Evaporation of the mixture and treatment with dilute aqueous sulphuric acid (10 ml) gave, with washing with chloroform, a yellow salt (0.45g) which on basification with dilute aqueous sodium hydroxide yielded 7-amino-1-methyl-3-phenylquinoxalin-2(1H)-one (385a) (0.34g, 68%), as yellow needles, m.p. 215-216° (from ethanol-dimethylformamide), $\nu_{max.}$ 3450, 3350, 3200 (NH_2), 1635 (CO) and 1615 (NH deformation) cm^{-1}, τ [$(CD_3)_2SO$] 1.69-1.85 (2H, m, ArH), 2.48 (1H, d, J_{ortho} 9 Hz, H-5),

2.52-2.66 (3H, m, ArH), 3.32 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-6), 3.49 (1H, d, J_{meta} 2 Hz, H-8), 3.84 (2H, br, NH_2) and 6.44 (3H, s, NMe).

Found: C,72.0%; H,5.3%; N,16.8%; M^+ 251.

$C_{15}H_{13}N_3O$ requires: C,71.7%; H,5.2%; N,16.7%; M 251.

Extraction of the filtrate with chloroform gave a purple intractable gum (1.00g). Basification of the aqueous layer with dilute aqueous sodium hydroxide and extraction with chloroform gave a red intractable gum (0.11g).

23. The Reaction of the Betaines (371 a and b) and (392a) with Piperidine.

The betaine (371 a or b) or (392a) (0.002 mol) in piperidine (40 ml) and methanol (6.0 ml) was heated under reflux for 1-5h. The mixture was cooled and any unreacted starting material was collected. Evaporation of the mixture gave a red oil which was treated with dilute aqueous sulphuric acid (10 ml) and extracted with chloroform (A). The aqueous layer was adjusted to pH 11 by the addition of dilute aqueous sodium hydroxide, extracted with chloroform (B) and the black intractable solid collected (C). The aqueous layer was neutralised carefully with dilute aqueous sulphuric acid and sodium acetate to give the product (374 a or b) or (385c).

(i) The N-methyl-betaine (371a) (0.50g) after heating under reflux for 5h gave starting material (0.27g, 55%) as an insoluble yellow solid, identical (i.r. spectrum) to an authentic sample. Work up of the filtrate as described above gave no product on neutralisation. Constant chloroform extraction of the neutral aqueous layer gave 7-amino-1-methylquinoxaline-2(1H),3(4H)-dione (374a) (0.05g, 13%; 29% based on unrecovered starting material), as yellow needles, m.p. 303-305° (decomp.) (from ethanol-dimethylformamide), $\nu_{max.}$ 3350 and 3250 (NH_2), 3100-2500 (OH), 1690 and 1650 (CO) and 1620 (NH deformation).

Found: C,55.9%; H,4.6%; N,21.6%; M^+191.

$C_9H_9N_3O_2$ requires: C,56.5%; H,4.7%; N,22.0%; M 191.

The chloroform extracts (A) and (B) gave intractable red oils (total 0.16g) and (C) was an intractable black solid (0.09g).

(ii) The N-benzyl-betaine (371b) (0.66g) heated under reflux for 1h gave as an insoluble solid 7-amino-1-benzylquinoxaline-2(1H), 3(4H)-dione (374c) (0.14g, 26%), yellow plates, m.p. 290-292° (decomp.) (from aqueous dimethylformamide), $\nu_{max.}$ 3450, 3350 and 3200 (NH_2), 3100-2500 (OH), 1700 and 1680 (CO) and 1620 (NH deformation) cm^{-1}.

Found: C,66.9%; H,5.0%; N,15.9%; M^+267.

$C_{15}H_{13}N_3O_2$ requires: C,67.4%; H,4.9%; N,15.7%; M 267.

The chloroform extract (A) gave a brown intractable oil (0.06g), the chloroform extract (B) gave a dark red intractable oil (0.25g) and (C) was a black intractable solid (0.20g).

(iii) The 3-phenyl-betaine (392a) (0.60g) heated under reflux for 1h gave as an insoluble solid 7-amino-3-phenylquinoxalin-2(1H)-one (385c) (0.10g, 21%), brown needles, m.p. 296-298° (decomp.) (from aqueous dimethylformamide), $\nu_{max.}$ 3450, 3350 and 3200 (NH_2), 3100-2500 (OH), 1660 (CO) and 1625 (NH deformation), τ $[(CD_3)_2SO]$ 1.62-1.82 (2H, m, ArH), 2.46-2.69 (4H, m, ArH), 3.38 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H-6), 3.60 (1H, d, J_{meta} 2 Hz, H-8) and 3.80-4.03 (2H, br, NH_2).

Found: C,69.9%; H,4.8%; N,17.7%; M^+237.

$C_{14}H_{11}N_3O$ requires: C,70.9%; H,4.7%; N,17.7%; M 237.

The chloroform extract (A) gave a dark red intractable oil (0.12g), the chloroform extract (B) gave a dark red oil containing piperidine (0.43g) and (C) was an intractable black solid (0.25g).

24. The Sandmeyer Reactions of the Amines (374b) and (374c).

A solution of cuprous chloride was prepared by dissolving hydrated

copper sulphate (0.62g) and sodium chloride (0.16g) in warm water (2.2 ml) and treating the solution dropwise with a solution of sodium metabisulphite (0.15g) in water (1.6 ml) over a period of 5 min. The mixture was cooled in ice and the supernatant liquid was decanted. The colourless residue was washed with water (containing a little sulphurous acid) by decantation and finally dissolved in concentrated hydrochloric acid (1.1 ml) and cooled in ice. The amine (374b) or (374c) (0.002 mol) was diazotised at 0° in 6N hydrochloric acid (2.0 ml) by dropwise addition with stirring of a solution of sodium nitrite (0.15g) in water (0.4 ml). The cold diazonium solution was mixed with the cold cuprous chloride solution with shaking and the mixture was warmed to room temperature and finally heated at 60° for 20 min.

(i) The mixture from 6-amino-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (374b) (0.41g) gave, on dilution with water (6.0 ml), cooling and scratching, 6-chloro-1,4-dimethylquinoxaline-2(1H),3(4H)-dione (367a) (0.31g, 70%), as a yellow solid, m.p. 183-188°, identical (m.p., mixed m.p. and i.r. spectrum) to a sample prepared as described in 8(i) above.

(ii) The mixture from 7-amino-1-benzylquinoxaline-2(1H),3(4H)-dione (374c) (0.54g) gave no solid on cooling. Neutralisation with solid sodium acetate gave a brown solid (0.13g), $\nu_{max.}$ 3400 br (OH), 2200 ($N\equiv N^+$) and 1670 (CO) cm^{-1}. Attempted crystallisation of this solid from ethanol-dimethylformamide gave a brown intractable solid (0.10g), $\nu_{max.}$ 3400 (OH) and 1660 (CO) cm^{-1}. This solid was insoluble in boiling dimethylformamide and could not be characterised.

On standing, the original aqueous filtrate gave a pale brown solid (0.12g), $\nu_{max.}$ 3450 (OH), 2200w ($N\equiv N^+$) and 1690 br (CO) cm^{-1} which was crystallised from ethanol-glacial acetic acid to give an unidentified brown solid (0.06g), $\nu_{max.}$ 3450 (OH) and 1690 br (CO) cm^{-1}, which was not investigated further.

25. The Preparation of the Phenol (385b).

7-Amino-1-methyl-3-phenylquinoxalin-2(1H)-one (385a) (0.25g, 0.001 mol) was dissolved in aqueous sulphuric acid (0.22 ml of concentrated sulphuric acid in 0.30 ml of water), treated with crushed ice (0.4g), cooled to 0° and diazotized by the dropwise addition, with mechanical stirring, of a solution of sodium nitrite (0.08g) in water (0.16 ml) over a period of 10 min. The mixture was allowed to reach room temperature, diluted with water (1.0 ml) and heated at 95° for 10 min. The mixture was cooled to give a yellow diazonium salt (0.23g), $\nu_{max.}$ 2250m ($N\equiv N^{+}$) and 1675 (CO) cm^{-1}, which decomposed on attempted recrystallisation from aqueous ethanol to give an intractable brown solid.

The yellow diazonium salt (0.1g) in dilute aqueous sulphuric acid (2.0 ml) was heated under reflux for 20 min. and the solution was cooled to give a pale brown solid (0.06g) which on crystallisation from ethanol-dimethylformamide gave 7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (385b) (0.03g, 28%), m.p. 295-300° (lit.,[231] 300°), identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample.

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APPENDIX

General Experimental Data

Unless otherwise stated, infrared spectra were measured for nujol suspensions using a Pye-Unicam SP200 Spectrophotometer. Bands were strong and sharp, unless otherwise specified (w) as weak, (m) as medium or (br) as broad.

Nuclear magnetic resonance spectra were measured at 100 MHz using a Varian H.A.100 instrument or at 60 MHz using a Varian E.M.360 instrument. Signals were sharp unless otherwise specified (br) as broad; s = singlet; d = doublet; dd = double doublet; t = triplet; dt = double triplet; q = quartet; m = multiplet. In all cases tetramethylsilane was used as internal standard.

Mass spectra and High Resolution Mass Spectral Analyses were measured at 70 eV using an A.E.I. MS902 instrument by Mr. D. Thomas, Chemistry Department, University of Edinburgh.

Microanalyses were carried out by Mr. J. Grunbaum, Department of Chemistry, University of Edinburgh, and also by the National Physical Laboratory, Teddington. Melting points of all analytical samples were determined using a Koffler hot-stage microscope and are uncorrected.

All organic extracts were dried over anhydrous magnesium sulphate, prior to evaporation under reduced pressure. Unless otherwise specified, solvents were of technical grade. Benzene was sodium-dried and light petroleum had b.p. 60-80°.

Thin layer chromatography (t.l.c.) was carried out over silica [Merck Kieselgel G.F.$_{254}$ (Type 60)] or alumina [Merck G.F.$_{254}$ (Type E)], unless otherwise stated.

Preparative thin layer chromatography was carried out over silica [Merck Kieselgel G.F.$_{254}$ (Type 60), activity III].

Dry-column chromatography was carried out over silica [Fison's (80-200 mesh), activity III] or alumina [Spence Type H, activity III].

Wet-column chromatography was carried out over silica [Fison's (80-200 mesh)] or alumina [Spence Type H].

A New Heterocyclisation Reaction Leading to Cinnolin-4(1*H*)-one Derivatives

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A New Heterocyclisation Reaction Leading to Cinnolin-4(1*H*)-one Derivatives

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Summary 2-Nitrophenacylidene phenylhydrazones (**2**) undergo base-catalysed cyclisation by intramolecular nucleophilic displacement of the nitro-group by the *ortho*-side-chain, providing an efficient general route to 3-substituted 1-phenylcinnolin-4(1*H*)-ones (**3**).

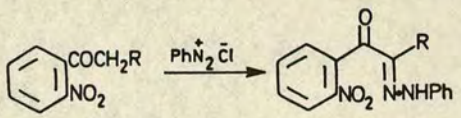
HETEROCYCLISATIONS involving the intramolecular nucleophilic displacement of the nitro-group in certain *ortho*-nitrobenzoyl derivatives have recently been described.[1] Analogous displacements in 2-nitrobenzylidene hydrazones provide a general method for the synthesis of indazole derivatives.[2] The application of cyclisations of this type to the synthesis of six-membered heterocycles is now reported in a new synthesis of cinnoline derivatives from 2-nitrophenacylidene phenylhydrazones.†

TABLE

3-Substituted 1-phenylcinnolin-4(1*H*)-ones.

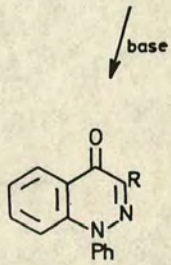
Compound	Yield/%	M.p./°C
(**3c**)	98	294
(**3d**)	76	276
(**3e**)	71	152
(**3f**)	91	224
(**3g**)	37	190

The 2-nitrophenacylidene phenylhydrazones (**2**) used as substrates were readily synthesised in high yield (80—100%) by coupling benzenediazonium chloride with 2-substituted *ortho*-nitroacetophenone derivatives (**1**) containing a suitably activated methylene group. Heating the hydrazone (**2a**) (0·016 mol) with 0·5M aqueous sodium carbonate (40 ml) in ethanol (60 ml) for 1 h afforded



(1) (2)

R	
a;	Ac
b;	Bz
c;	$CONH_2$
d;	SO_2Ph
e;	CO_2Et
f;	CN
g;	NO_2
h;	CO_2H
i;	OBz
j;	OH



(3)

3-acetyl-1-phenylcinnolin-4(1*H*)-one (**3a**) (92%), m.p. 165°, whose structure follows from its oxidation by chromic acid or sodium hypochlorite to the known[3] carboxylic acid (**3h**) (58—83%), m.p. 275°. The structure of the phenyl ketone (**3b**) (81%), m.p. 183°, derived from the hydrazone **2b**), was also established by Baeyer-Villiger oxidation (30%)

† Satisfactory analyses and spectral data were obtained for all new compounds.

aqueous hydrogen peroxide–glacial acetic acid) which occurred by preferential migration of the heterocyclic nucleus, affording the benzoate (**3i**) (70%), m.p. 165°, and the parent hydroxy-compound (**3j**) (18%), m.p. 227°. Sodium carbonate also catalysed the cyclisation of the hydrazones (**2c**—**e**) to the cinnolinones (**3c**—**e**) in high yield (Table).

The transformations of the hydrazones (**2a**—**e**) into the cinnolinones (**3a**—**e**) are intramolecular nucleophilic aromatic substitution reactions involving the displacement of a nitro-group by a nitrogen nucleophile. The ready cyclisation of the cyano- and nitro-hydrazones (**2f**) and (**2g**) to the corresponding cinnolinones (**3f**) and (**3g**) (Table) in warm aqueous ethanolic sodium acetate shows the ease of the heterocyclisation [(**2**) → (**3**)] and contrasts with the less ready cyclisation of 2-nitrobenzylidene hydrazones to indazoles.[2]

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